

**Supplementary Note**  
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**“Genome-Wide Association Study of Schizophrenia Identifies Five Novel Loci”**

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## A. Recruitment and Assessment of Subjects.

**Combined PGC GWAS Cases and Controls (Stage 1):** Individuals of European ancestry with schizophrenia or schizoaffective disorder were included since family studies have shown familial coaggregation of schizophrenia and schizoaffective disorder<sup>1</sup>, diagnostic criteria separating these two disorders are subjective, and the inter-rater reliability is often low across research groups<sup>2</sup>. 9,394 European ancestry cases were collected with institutional review board approval at numerous clinical centers in 17 samples representing 11 countries (Australia, Bulgaria, Denmark, Germany, Ireland, Netherlands, Norway, Portugal, Sweden, United Kingdom, and United States of America).

The quality of phenotypic data was verified by a systematic review of data collection methods at each site (Table S13). Furthermore, to assess the quality of the phenotypic assessment in the various GWAS studies, one of us with extensive prior experience in field studies of schizophrenia (KSK) developed an 18-item questionnaire, covering in considerable detail the nature of the assessment protocol and associated QC procedures. All participating studies completed this questionnaire. By consensus, nine key items were selected for the further evaluation of each study. These items were: i) the use of a structured psychiatric interview, ii) systematic training of interviewers in the use of the instrument, iii) systematic QC of diagnostic accuracy, iv) reliability trials, v) review of medical record information, vi) best-estimate procedure employed, vii) specific inclusion and exclusion criteria developed and utilized, viii) MDs or PhDs as making the final diagnostic determination, and ix) special additional training for the final diagnostician. Each study was given a score on this scale. On the initial assessment, all but 4 studies met at least 7 of the 9 criteria and were judged of high quality. Two studies were further queried and adequate documentation was provided to assure high diagnostic quality. One study (ISC – SW1-2) used a fundamentally different ascertainment methodology. Further empirical support for the validity of this approach was requested, provided<sup>3</sup>, and approved by the group. One other study was excluded due to inadequate QC of the diagnostic process.

Controls consisted of 12,462 samples of European ancestry collected from the same countries. As the prevalence of schizophrenia is low, a large control sample where some controls were not screened for schizophrenia was utilized.

**Replication samples (Stage 2):** 8,442 European ancestry cases were collected with institutional review board approval at numerous clinical centers in 19 samples representing 14 countries (Australia, Belgium, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Russian Federation, Sweden, United Kingdom, and United States of America). Controls consisted of 21,397 samples of European ancestry collected from the same countries. Genotyping and association analyses are described further below for the Stage 2 samples with focused genotyping.

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### 1. Detailed Stage 1 (GWAS) Named Sample Descriptions

1. Cardiff UK
2. CATIE
3. ISC - Aberdeen

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4. ISC - Cardiff
5. ISC - Dublin
6. ISC - Edinburgh
7. ISC - London
8. ISC - Portugal
9. ISC - SW1
10. ISC - SW2 – with GWAS 9 (ISC - SW1)
11. MGS
12. SGENE - Bonn
13. SGENE - Copenhagen
14. SGENE - Munich
15. SGENE - TOP3
16. SGENE - UCLA
17. Zucker Hillside

Further details regarding these samples are tabulated in Tables 1, S1, and S3.

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### **Stage 1: GWAS – European ancestry sample 1 – Cardiff UK**

**Cases:** The GWAS sample of 479 cases (324 males and 155 females) has been previously described <sup>4</sup>; 472 of these cases (320 males and 152 females) were included in the present study. All were Caucasian and born in the British Isles. The Multicentre Research Ethics Committee (MREC Wales) approved the study, as did Local Research Ethics Committees (LRECs) from all sites at which cases were recruited, and all cases gave written informed consent to participate.

**Controls:** The control sample is that used by the Wellcome Trust Case Control Consortium (WTCCC) described in detail elsewhere <sup>5</sup>. Briefly, 2,937 controls (1,445 males and 1,492 females), of whom 2,934 (1,442 males and 1,492 females) were included in the present study, came from two sources (similar N from each source): the 1958 British Birth Cohort (58C) and from a panel of UK consenting blood donors (UKBS) established specifically for the WTCCC study. At a genome wide level, the two groups do not significantly differ with respect to allele frequencies justifying their use as a single control group. Individuals (N=26) with non-Caucasian ancestry as determined by Multidimensional Scaling (MDS) were previously removed by the WTCCC from the sample. Approval for use of the control data for this study was obtained by the PGC.

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### **Stage 1: GWAS – European ancestry sample 2 – CATIE**

**Cases:** The case sample was collected as part of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, and ascertainment was previously described <sup>6-8</sup>. It is comprised of 738 of the 1,460 CATIE participants donating a DNA sample – cases (544 males and 194 females) from multiple sites in the United States of America (USA) of which 402 European ancestry cases (308 males and 94 females) were used in the stage 1 GWAS here. Cases gave written informed consent, and the

institutional review boards (IRBs) at each of the CATIE sites, and the IRB at the University of North Carolina (Chapel Hill, NC), approved the human subjects protocol.

**Controls:** The control sample used for the CATIE GWAS was collected by MGS (see controls description below for Stage 1: GWAS – European ancestry sample 11 – MGS)<sup>9-11</sup>. In the CATIE GWAS, the utilized MGS controls totaled 733 (493 males and 240 females). After removing duplicate controls already represented in the MGS GWAS and those who were not of European ancestry, 207 (161 males and 46 females) of the MGS-collected controls genotyped in the CATIE GWAS remained and were used in the stage 1 European ancestry GWAS here. Controls gave online informed consent, have been fully anonymized, and the NorthShore University HealthSystem's IRB approved the human subjects protocol (as did the IRB at the University of North Carolina for the CATIE GWAS aspect of these controls' utilization).

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### **Stage 1: GWAS – European ancestry sample 3 – ISC - Aberdeen**

**Cases:** The case sample ascertainment has been previously described<sup>12,13</sup>. 720 cases (536 males and 184 females) born in the British Isles (95% in Scotland) were used in the PGC GWAS. All cases gave written informed consent, and both local and multiregional academic ethical committees approved the human subjects protocol.

**Controls:** The control sample ascertainment has been previously described<sup>12,13</sup>. 698 controls (447 males and 251 females) were used in the PGC GWAS. Controls gave written informed consent, and both local and multiregional academic ethical committees approved the human subjects protocol.

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### **Stage 1: GWAS – European ancestry sample 4 – ISC - Cardiff**

**Cases:** The case sample ascertainment has been previously described<sup>12,13</sup>. It is comprised of 584 cases born in Bulgaria (297 males and 287 females), of which 527 (270 males and 257 females) were used in the PGC GWAS. Cases gave written informed consent, and the local ethics committee from all the regions where cases were recruited approved the human subjects protocol.

**Controls:** The control sample has been previously described<sup>12,13</sup>. It is comprised of 705 controls born in Bulgaria (349 males and 356 females), of which 609 (291 males and 318 females) were used in the PGC GWAS. Controls gave written informed consent, and local ethics committees at the hospitals where the subjects were recruited approved the human subjects protocol.

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### **Stage 1: GWAS – European ancestry sample 5 – ISC - Dublin**

**Cases:** The case sample was collected primarily in the Dublin area, and ascertainment has been previously described<sup>12,13</sup>. It is comprised of 280 cases of Irish origin (197 males and 83 females), of which 270 (188 males and 82 females) were used



in the PGC GWAS. Cases gave written informed consent, and the Ethics Committee at all participating hospitals and centers approved the human subjects protocol.

**Controls:** The control sample has been previously described <sup>12,13</sup>. It is comprised of 914 controls of Irish origin (275 males and 639 females), of which 860 (258 males and 602 females) were used in the PGC GWAS. Controls gave written informed consent, and the Federated Dublin Hospitals & Irish Blood Transfusion Services Ethics Committees approved the human subjects protocol.

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### **Stage 1: GWAS – European ancestry sample 6 – ISC - Edinburgh**

**Cases:** The case sample was collected from southeast Scotland, and ascertainment has been previously described <sup>12,13</sup>. It is comprised of 403 Caucasian cases from Scotland (294 males and 109 females) of which 368 (267 males and 101 females) were used in the PGC GWAS. Cases gave written informed consent, and the Scotland A Research Ethics Committee approved the human subjects protocol.

**Controls:** The control sample has been previously described <sup>12,13</sup>. It is comprised of 339 (174 males and 165 females) controls from the same region of Scotland (as the cases), of which 284 (146 males and 138 females) were used in the PGC GWAS. Controls gave written informed consent, and the human subjects protocol was approved by the Scotland A Research Ethics Committee.

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### **Stage 1: GWAS – European ancestry sample 7 – ISC - London**

**Cases:** The case sample ascertainment has been previously described <sup>12,13</sup>. It is comprised of 617 cases for whom both parents were English, Scottish, or Welsh, with additional grandparental and medical record confirmation of ancestry (432 males and 185 females), of which 518 (369 males and 149 females) were used in the PGC GWAS. Cases gave written informed consent, and the U.K. National Health Service (NHS) multicenter and local research ethics committee approved the human subjects protocol.

**Controls:** The control sample was collected by the University College London (UCL) molecular psychiatry lab and has been previously described <sup>12,13</sup>. It is comprised of 661 controls for whom both parents were English, Scottish, or Welsh, with additional grandparental and medical record confirmation of ancestry (296 males and 365 females), of which 491 (207 males and 284 females) were used in the PGC GWAS. Controls gave written informed consent, and the U.K. National Health Service (NHS) multicenter and local research ethics committee approved the human subjects protocol.

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### **Stage 1: GWAS – European ancestry sample 8 – ISC - Portugal**

**Cases:** Cases lived in Portugal, the Azorean and Madeiran islands, or were the direct (first or second generation) Portuguese immigrant population in the USA, as previously described <sup>14</sup>. 346 cases (213 males and 133 females) were used in this

analysis. Cases gave written informed consent, and the IRB of SUNY Upstate Medical University (Syracuse, New York) approved the human subjects protocol.

**Controls:** Controls were not related to cases, with the exception of 3 controls that married into families but were not biologically related to cases. The control sample used in this analysis was comprised of 215 controls (80 males and 135 females). Like the cases, they also lived in Portugal, the Azorean and Madeiran islands, or were the direct (first or second generation) Portuguese immigrant population in the USA. Controls gave written informed consent, and the IRB of SUNY Upstate Medical University (Syracuse, New York) approved the human subjects protocol.

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#### **Combined sample description for:**

**Stage 1: GWAS – European ancestry sample 9 – ISC - SW1**

**Stage 1: GWAS – European ancestry sample 10 – ISC – SW2**

**Stage 2: Replication follow-up – European ancestry sample 16 – SW3**

**Stage 2: Replication follow-up – European ancestry sample 17 – SW4**

**Cases:** The case sample was identified by having a discharge diagnosis (92% with  $\geq 2$  admissions) of schizophrenia in the Swedish national Hospital Discharge Register; ascertainment has been previously described further<sup>12,13</sup>. We have previously shown that this definition of illness yields recurrence risks to relatives essentially identical to those via other approaches<sup>3</sup>. Included here are 558 cases (168 for SW1 and 390 for SW2 genotyping waves) used in the PGC GWAS (SW1 with 93 males and 75 females, and SW2 with 231 males and 159 females). Cases from SW3 (N=539, consisting of 327 males and 212 females) and SW4 (N=1,063, consisting of 656 males and 407 females) were included as part of the replication effort. SW1-4 refers to genotyping batch (SW1 being the earliest and SW4 the most recent) in this on-going study. For 111 of the first 121 consecutive cases, electronic medical record review using a structured DSM-IV<sup>15</sup> checklist for schizophrenia was conducted (C.H.), and substantiated the presence of DSM-IV schizophrenia in 95.5% (106/111) of these cases. The Karolinska Institutet IRB approved the human subjects protocol, the health board to which the potential subject was registered gave permission to make contact with the subject, and the cases gave written informed consent.

**Controls:** The control sample has been previously described<sup>12,13</sup>. Controls were sampled proportionally from the same counties as cases. Ascertainment in the primary project is ongoing. Included here in the PGC GWAS are 167 controls (82 males and 85 females) from SW1, and 229 controls (116 males and 113 females) from SW2 genotyping waves. Controls from SW3 (N=905, consisting of 457 males and 448 females) and SW4 (N=1,173, consisting of 605 males and 568 females) were included as part of the replication effort. The Karolinska Institutet IRB approved the human subjects protocol, the health board to which the potential control was registered gave permission to make contact with the subject, and the controls gave written informed consent and were interviewed about other medical conditions.

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### **Stage 1: GWAS – European ancestry sample 11 – MGS**

**Cases:** The European ancestry case sample was collected by the MGS collaboration, and ascertainment is described in detail elsewhere<sup>9,10,16,17</sup>. It is comprised of 2,681 cases from the USA and Australia (1,865 males and 816 females) of which 2,679 (1,863 males and 816 females) were used in the combined GWAS. Cases gave written informed consent, and each collecting site's IRB approved the human subjects protocol.

**Controls:** A survey company (Knowledge Networks, under MGS guidance) collected the European ancestry control sample, and ascertainment is described in detail elsewhere<sup>9-11</sup>. It is comprised of 2,653 controls from the USA (1,269 males and 1,384 females) of which 2,484 (1,140 males and 1,344 females) were used in the combined GWAS. Controls gave online informed consent, have been fully anonymized, and the NorthShore University HealthSystem's IRB approved the human subjects protocol.

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### **Stage 1: GWAS – European ancestry sample 12 – SGENE - Bonn**

**Cases:** The case sample was ascertained as previously described<sup>18</sup> and is all of German descent. It is comprised of 474 cases (238 males and 236 females) that were used in the stage 1 GWAS here. Cases gave written informed consent, and the local ethical committees approved the human subjects protocol.

**Controls:** The German GWAS controls (previously described in part<sup>18</sup>) were drawn from three population-based epidemiological studies: (A) PopGen<sup>19</sup>, (B) the Cooperative Health Research in the Region of Augsburg (KORA) study<sup>20</sup>, and (C) the Heinz Nixdorf Recall (HNR) study<sup>21</sup>. The recruitment areas for PopGen were located in Northern Germany, for KORA in Southern Germany, and for HNR in Central Western Germany. Post-QC genotypes of 1,304 controls (664 males and 640 females) were used in the stage 1 GWAS here. Controls gave written informed consent, and the local ethical committees approved the human subjects protocol.

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### **Combined sample description for:**

#### **Stage 1: GWAS – European ancestry sample 13 – SGENE – Copenhagen**

#### **Stage 2: Replication follow-up – European ancestry sample 5 – SGENE - Copenhagen**

**Cases:** The case sample was previously described<sup>22</sup>. It is comprised of 944 cases (544 males and 400 females) from the Copenhagen area of Denmark, of which 482 (280 males and 202 females) were used in the GWAS and 462 in the replication study (264 males and 198 females). Cases gave written informed consent, and the human subjects protocol was approved by the Danish Scientific-Ethical Committee (J. no. 01-024/01) and by the Danish Data Protection Agency (J. no. 2001-54-0798).

**Controls:** The control sample, age and gender matched to the case sample, was collected as previously described<sup>23</sup>. It is comprised of 1,331 controls (767 males and 564 females) of whom 892 were randomly selected among 15,000 subjects in the Danish Blood donor corps in Copenhagen, and 439 population control samples were collected from the Copenhagen area by the Danish Headache Center. Of these subjects, 457 blood donor controls (268 males and 189 females) were used in the GWAS, while 874 control subjects (435 blood donors and 439 population controls) were used in the replication study (499 males and 375 females). Controls gave informed consent, and the human subjects protocol was approved by the Danish Scientific-Ethical Committee (J. no. 01-024/01) and by the Danish Data Protection Agency (J. no. 2001-54-0798).

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#### **Combined sample description for:**

**Stage 1: GWAS – European ancestry sample 14 – SGENE – Munich**

**Stage 2: Replication follow-up - European ancestry sample 12 – SGENE - Munich**

**Stage 2: Replication follow-up - European ancestry sample 13 – SGENE - Munich**

Note that the descriptions below are for the three components of the SGENE - Munich sample included in the current study, namely, the stage 1 GWAS portion (434 cases, 351 controls), and the stage 2 replication portion comprised of GWAS genotyped samples (163 cases, 185 controls) plus samples with focused genotyping (303 cases, 1,614 controls).

**Cases:** The case sample was collected by Rujescu and colleagues, and ascertainment has been described<sup>24</sup>. It is comprised of 900 cases from Germany and Central Europe (559 males and 341 females), of which 434 (279 males and 155 females) were used in the GWAS and 466 (280 males and 186 females) in the replication study. For the replication study, 200 initial cases with GWAS genotypes yielded 163 after QC, and 311 initial cases with focused genotyping yielded 303 after QC. Cases gave written informed consent, and the human subjects protocol was approved by the IRB.

**Controls:** The control sample was collected by Rujescu and colleagues from the general population of Munich, and has been described<sup>25</sup>. It is comprised of 2,150 controls from Germany (1,054 males and 1,096 females), of which 351 (167 males and 184 females) were used in the GWAS and 1,799 (887 males and 912 females) in the replication study. For the replication study, 200 initial controls with GWAS genotypes yielded 185 after QC, and 1,633 initial controls with focused genotyping yielded 1,614 after QC. Controls gave written informed consent, and the human subjects protocol was approved by the IRB.

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**Stage 1: GWAS – European ancestry sample 15 – SGENE - TOP3**

**Cases:** The Thematically Organized Psychosis (TOP) Study group collected the case sample, born in Norway, from Oslo <sup>26</sup>. It is comprised of 277 cases of which n=248 were used in the GWAS (132 males and 116 females). The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study, and the Norwegian Directorate of Health approved the biobank.

**Controls:** The TOP Study group also randomly selected from the national records at Statistics Norway ([www.ssb.no](http://www.ssb.no)) the control sample from the same catchment areas as the cases <sup>26</sup>. The sample is comprised of 371 controls from Norway (184 males and 187 females) of which n=351 were used in the GWAS (176 males and 175 females). Controls gave written informed consent, and the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study, and the Norwegian Directorate of Health approved the biobank.

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### **Stage 1: GWAS – European ancestry sample 16 – SGENE - UCLA**

**Cases:** The case sample was collected by Utrecht and GROUP investigators, as previously described <sup>18,24</sup>. It is comprised of 758 (571 males and 187 females) cases of Dutch ancestry (based on their grandparents being born in The Netherlands), of which 704 (529 males and 175 females) were used in the GWAS. Cases gave written informed consent, and local IRB committees at UCLA (Los Angeles) and UMC Utrecht approved the human subjects protocol.

**Controls:** The control sample was collected by Utrecht and GROUP investigators, as previously described <sup>18,24</sup>. It is comprised of 672 controls (331 males and 341 females) of Dutch ancestry (based on their grandparents being born in The Netherlands), of which 631 (310 males and 321 females) were used in the GWAS. Controls gave written informed consent, were assessed with the CASH <sup>27</sup>, and local IRB committees at UCLA (Los Angeles) and UMC Utrecht approved the human subjects protocol.

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### **Stage 1: GWAS – European ancestry sample 17 – Zucker Hillside**

**Cases:** The case sample was collected as described previously <sup>28</sup>. It is comprised of 192 cases (128 males and 64 females) from the New York metropolitan area, specifically Queens and Nassau County. All cases gave written informed consent, and the IRB of the North Shore – LIJ Health System approved the human subjects protocol.

**Controls:** Dr. Anil Malhotra and colleagues also collected the control sample, as described previously <sup>28</sup>. It is comprised of 190 controls (92 males and 98 females) from the New York metropolitan area. All controls gave written informed consent, and the human subjects protocol was approved by the IRB of the North Shore – LIJ Health System.

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## 2. Detailed Stage 2 (Replication) Named Sample Descriptions

1. Multicenter-Pedigree
2. SGENE - Aarhus
3. SGENE - Aarhus
4. SGENE – Belgium
5. SGENE - Copenhagen – with GWAS 13 (SGENE - Copenhagen)
6. SGENE – Iceland
7. SGENE – England
8. SGENE – Helsinki
9. SGENE – Hungary
10. SGENE – Italy
11. SGENE - Kuusamo – with Replication 8 (SGENE - Helsinki)
12. SGENE - Munich -- with GWAS 14 (SGENE - Munich)
13. SGENE - Munich -- with GWAS 14 (SGENE - Munich)
14. SGENE – Russia
15. SGENE – Sweden
16. SW3 – with GWAS 9 (ISC - SW1)
17. SW4 – with GWAS 9 (ISC - SW1)
18. University of Queensland (and Australian Schizophrenia Research Bank)
19. Irish Schizophrenia Genomics Consortium and WTCCC2

Further details regarding these samples are tabulated in Tables 1, S2, and S3.

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### Stage 2: Replication follow-up – European ancestry sample 1 – Multicenter-Pedigree

**Cases (and their families):** The case family sample was collected by separate research projects in Europe, Australia, and the USA, using previously described methods of ascertainment and clinical assessment<sup>16,29-37</sup>, with further summary description in a recent joint SNP genomewide linkage scan<sup>38</sup>. In all analyses presented here, cases with schizophrenia or schizoaffective disorder were considered affected, due to familial co-segregation<sup>39</sup> and the difficulty of reliable differentiation<sup>2</sup>. All other family members were considered “diagnosis unknown”. Siblings who were diagnosed by the contributing site with a schizophrenia spectrum disorder (other non-affective psychoses, schizotypal personality disorder, or paranoid personality disorder) were only included (as “unknown” diagnosis) if no parent or unaffected sibling had been genotyped. The Multicenter-Pedigree case family sample used for the Stage 2 replication here is comprised of 583 European-ancestry families with constellations informative for family-based association analysis (TRANSMIT<sup>40</sup>). Genotyped individuals (N=2,204) included 1,212 affected cases (777 males and 435 females, an average of 2.1 per family) and 992 additional relatives as described above (450 males, 542 females). Cases gave informed consent, and the appropriate human subjects committee for each site approved the human subjects protocol.

**Controls:** Multicenter-Pedigree was a family-based sample with no unrelated controls.

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## Stage 2: Replication follow-up – European ancestry sample 2 – SGENE - Aarhus

**Cases:** The case sample was collected through the Danish Newborn Screening Biobank ([www.ssi.dk](http://www.ssi.dk)), with ascertainment through the Danish Psychiatric Central Register<sup>41</sup>. It is comprised of 909 cases from Denmark, and after QC, 876 cases (477 males and 399 females) remained that were used in the replication study. The Danish Data Protection Agency and the ethics committees in Denmark approved the human subjects protocol.

**Controls:** The control sample was collected through the Danish Newborn Screening Biobank ([www.ssi.dk](http://www.ssi.dk)) to match the case sample by birth cohort, with ascertainment through Danish Psychiatric Central Register<sup>41</sup>. It is comprised of 899 controls from Denmark, and after QC, 874 controls (477 males and 397 females) remained that were used in the replication study. The Danish Data Protection Agency and the ethics committees in Denmark approved the human subjects protocol.

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## Stage 2: Replication follow-up – European ancestry sample 3 – SGENE - Aarhus

**Cases:** The case sample was ascertained through psychiatric departments and twin pair studies, and was of Danish parentage three generations back. The sample is comprised of 236 cases (193 incident cases and 43 cases ascertained from twin pairs). After QC and removal of cases included in the genome-wide typed Denmark (Copenhagen) or Denmark (Aarhus) samples, 217 cases (114 males, 102 females, and 1 sex unknown) remained for use in the replication study. Cases gave written informed consent, and the Danish Data Protection Agency and the ethics committees in Denmark approved the human subjects protocol.

**Controls:** The control sample was collected at the University of Aarhus, and is comprised of 500 medical students, all of Danish parentage three generations back. After QC and removal of samples included in the genome-wide typed Denmark (Copenhagen) or Denmark (Aarhus) samples, 493 controls (176 males and 317 females) remained for use in the replication study. Controls gave written informed consent, and the Danish Data Protection Agency and the ethics committees in Denmark approved the human subjects protocol.

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## Stage 2: Replication follow-up – European ancestry sample 4 – SGENE - Belgium

**Cases:** The previously described<sup>42</sup> case sample is comprised of 521 cases (334 males, 183 females, and 4 missing sex information). After QC, 510 cases (326 males, 180 females, and 4 missing sex information) remained for analysis in the replication study. Cases provided written, informed consent for participation and approval was obtained from the ethics committee.

**Controls:** The control sample was collected as previously described<sup>43</sup>. It is comprised of 341 Flemish controls (149 males and 192 females), of which all were used in the replication study. Controls provided written, informed consent for participation and approval was obtained from the ethics committee.



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## **Stage 2: Replication follow-up – European ancestry sample 6 – SGENE - Iceland**

**Cases:** The case sample is comprised of 569 cases (365 males and 204 females) from all over Iceland. After completion of QC, 531 cases (346 males and 185 females) remained for analysis in the replication study. Cases provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

**Controls:** The control sample was recruited as a part of various genetic programs at deCODE. It is comprised of 12,047 controls (5,939 males and 6,108 females) from all over Iceland. After completion of QC, 11,615 controls (5,802 males and 5,813 females) remained for analysis in the replication study. Controls provided written informed consent for participation, and the human subjects protocol approval was obtained from the ethics committees at each location.

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## **Stage 2: Replication follow-up – European ancestry sample 7 – SGENE - England**

**Cases:** The case sample was drawn from the Maudsley Family Study of psychosis<sup>44</sup>, the psychosis twin study<sup>45</sup>, and the genetics and psychosis (GAP) study<sup>46</sup>. It is comprised of 118 cases (89 males and 29 females) from England. Following QC, 93 cases (71 males and 22 females) remained for analysis in the replication study. Cases provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

**Controls:** The control sample was collected by the Maudsley Family Study of psychosis<sup>44</sup>, the psychosis twin study<sup>45</sup>, and the genetics and psychosis (GAP) study<sup>46</sup>. It is comprised of 98 controls (52 males and 46 females) from England. Following QC, 88 controls (48 males and 40 females) remained for analysis in the replication study. Controls provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

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## **Combined sample description for:**

### **Stage 2: Replication follow-up – European ancestry sample 8 – SGENE – Helsinki**

### **Stage 2: Replication follow-up – European ancestry sample 11 – SGENE - Kuusamo**

**Cases:** The Finnish case sample was drawn from a nationwide collection of families with schizophrenia spectrum disorders. It is comprised of 200 cases (128 males and 72 females) from Finland. After QC, 182 cases (112 males and 70 females) remained for analysis in the replication study. Of the cases finally included, 123 were from Kuusamo, an internal isolate of Finland having a 3.0% age corrected lifetime risk for schizophrenia compared to 1.1% in the general population<sup>47</sup>, and 59 came from

outside of Kuusamo. Cases provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

**Controls:** The control sample was derived from the Health 2000 survey<sup>48,49</sup>. It is comprised of 200 controls (125 males and 75 females) from Finland. After QC, 197 controls (122 males and 75 females) remained for analysis in the replication study. Of the controls finally included, 50 were from Kuusamo and 147 were from outside of Kuusamo. Controls provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

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## **Stage 2: Replication follow-up – European ancestry sample 9 – SGENE - Hungary**

**Cases:** The case sample was collected in Budapest<sup>50</sup>. It is comprised of 280 cases (128 males and 152 females) from Hungary. Following QC, 241 cases (105 males and 136 females) remained for analysis in the replication study. Cases provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

**Controls:** The previously described<sup>50</sup> control sample is comprised of 230<sup>50</sup> (97 males and 133 females) from Hungary. Following QC, 214 controls (89 males and 125 females) remained for analysis in the replication study. Controls provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

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## **Stage 2: Replication follow-up – European ancestry sample 10 – SGENE - Italy**

**Cases:** The case sample was identified from the South Verona Case Register<sup>51</sup>. It is comprised of 94 cases (53 males and 41 females) from Verona, Italy. Of these, 84 cases (48 males and 36 females) remained following QC for analysis in the replication study. Cases provided written, informed consent for participation and approval was obtained from the local ethics committee.

**Controls:** Controls were volunteers randomly selected from repeat blood donors via the Blood Transfusion Service of Verona. The controls sample is comprised of 94 subjects (53 males and 41 females) from Verona, Italy. Of these, 89 controls (50 males and 39 females) remained following QC for analysis in the replication study. Controls provided written, informed consent for participation and approval was obtained from the local ethics committee.

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## **Stage 2: Replication follow-up – European ancestry sample 14 – SGENE - Russia**

**Cases:** The sample is comprised of 498 cases (140 males and 358 females) from Moscow, all ethnic Russians. After QC, 475 cases (132 males and 343 females) remained for analysis in the replication study. Cases provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

**Controls:** The control sample was randomly selected from the general population of Moscow. It is comprised of 500 controls (192 males and 308 females) from Moscow, all ethnic Russians. After QC, 468 controls (178 males and 290 females) remained for analysis in the replication study. Controls provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

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## **Stage 2: Replication follow-up – European ancestry sample 15 – SGENE - Sweden**

**Cases:** The case sample<sup>23</sup> was recruited from northwestern Stockholm County. It is comprised of 257 Caucasian cases (160 males and 97 females) from Sweden. Following QC, 252 cases (158 males and 94 females) remained for analysis in the replication study. Cases gave informed consent, and the human subjects protocol was approved by the ethical committee of the Karolinska Hospital and the Stockholm Regional Ethical committee.

**Controls:** The control sample was recruited either among subjects previously participating in biological psychiatric research at the Karolinska Institute or drawn from a representative register of the population in Stockholm County. The control sample is comprised of 293 Caucasian controls (182 males and 111 females) from Sweden. Following QC, 287 controls (178 males and 109 females) remained for analysis in the replication study. Controls provided written, informed consent for participation and approval was obtained from the ethics committees at each location.

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## **Stage 2: Replication follow-up – European ancestry sample 18 – University of Queensland and Australian Schizophrenia Research Bank**

The Australian replication sample consisted of three sub-sets (detailed below): (1) The Australian Schizophrenia Research Bank (ASRB); (2) Brisbane Psychosis Study; (3) Oxfordshire Healthy Blood Donor Controls. As detailed below, the final Australian dataset analyzed in the replication consisted of 1,515 individuals (834 males, 645 females, 36 unknown gender; cases 558, controls 957). Of the 558 cases, 347 were males, 190 were females, and 21 were of unknown gender. Of the 957 controls, 487 were males, 455 were females, and 15 were of unknown gender.

### **The Australian Schizophrenia Research Bank (ASRB):**

**Cases:** The case sample was recruited by V.J.C., S.V.C., A.V.J., C.M.L., C.P., and U.S. in four Australian States (New South Wales, Queensland, Western Australia and Victoria) through treatment settings, such as hospital inpatient units, community mental health services, outpatient clinics and rehabilitation services, non-government mental illness support organizations, and, in the initial stages, through a large-scale, national, multi-media advertising campaign conducted via television and radio community service advertisements, web pages and media interviews. Ascertainment is described briefly here. At the time of writing it is comprised of 493 cases from larger metropolitan centers of Brisbane, Newcastle, Sydney, Melbourne, and Perth (325 males and 168

females) of which 438 cases (270 males, 152 females, 16 unknowns) were used in the replication study. Cases gave written informed consent, and the human subjects protocol was initially approved by Hunter New England Area Health Research Committee and subsequently approved by relevant Institutional Ethics Committees in Brisbane, Sydney, Melbourne and Perth.

**Controls:** Healthy controls were recruited through multi-media advertisements, and other sources. The control sample was collected by V.J.C., S.V.C., A.V.J., C.M.L., C.P., and U.S. and is described briefly here. It is comprised of 293 controls from the metropolitan centers of Brisbane, Newcastle, Sydney, Melbourne, and Perth of which 282 controls (125 males; 150 females; 7 unknown) were used in the replication study. Controls gave written informed consent, and the human subjects protocol was approved by Hunter New England Area Health Research Committee. The study was subsequently approved by relevant local Institutional Ethics Committees in Brisbane, Sydney, Melbourne and Perth.

### **Brisbane Psychosis Study:**

**Cases:** The case sample was collected by J.J.M. and B.J.M. and ascertainment is described in the following publications<sup>52,53</sup>. It is comprised of 310 cases from Brisbane, Australia (overall sample; 185 males and 125 females) of which 120 cases (77 males, 38 females, 5 unknowns) were used in the replication study. Cases gave written informed consent and the human subjects protocol was approved by the Wolston Park Hospital Institutional Ethics Committee, Wacol, Brisbane.

**Controls:** The control sample was collected by J.J.M. and B.J.M. and is described in the following publications<sup>52,53</sup>. It is comprised of 303 controls from Brisbane, Australia (159 males and 144 females) of which 121 controls (76 males, 44 females, 1 unknown) were used in the replication study. Controls gave written informed consent, and the human subjects protocol was approved by Wolston Park Hospital Institutional Ethics Committee, Wacol, Brisbane.

### **Oxfordshire Healthy Blood Donor Controls:**

**Controls:** The control sample is described elsewhere<sup>54</sup>. It is comprised of 724 controls (364 males, 317 females, 43 unknown) from Oxfordshire, England of which 554 controls (286 males, 261 females, 7 unknown) were used in the replication study. Controls gave written informed consent. The human subjects protocol was initially approved by the Anglia and Oxford Multicentre Research Ethics Committee, and subsequently by the local Central Oxford Research Ethics Committee.

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### **Stage 2: Replication follow-up – European ancestry sample 19 – Irish Schizophrenia Genomics Consortium and WTCCC2**

**Cases:** The Irish sample is part of the Wellcome Trust Case Control Consortium 2 (WTCCC2<sup>55</sup>; [www.wtccc.org.uk/cc2](http://www.wtccc.org.uk/cc2)) investigation of common, complex genetic

disorders. The case sample used in this study included 1,310 cases (968 males and 342 females), all with four Irish grandparents, recruited in the Republic of Ireland and Northern Ireland. None of the individuals used here were included in the International Schizophrenia Consortium (ISC) GWAS<sup>13</sup>. Ethics committee approval was obtained from all participating hospitals and centers.

**Controls:** WTCCC2 controls (N =1,023; 245 males and 778 females), also not included in the ISC GWAS<sup>13</sup>, were ascertained with written informed consent from the Irish GeneBank and represented blood donors from the Irish Blood Transfusion Service (IBTS), whose Ethics Committee approved the human subjects protocol.

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### 3. Stage 1 Association Analyses with stricter control for population stratification

To further evaluate, if population stratification could be a possible source of the inflation of association-signal (GC-lambda), we performed several analyses with stricter control-thresholds:

3a. We excluded genetic outliers based on the first two PCs with the following values (compare with Figure S8):

- SGENE - Bonn: PC1 > 0.03
- SGENE - Copenhagen: PC1 > 0.01; PC2 < -0.01
- Cardiff UK: PA1 > 0.02; PA2 > 0.02
- SGENE - Munich: PC1 > 0.03; PC2 < -0.01
- SGENE - TOP3: PC1 > 0.01; PC2 < -0.01
- SGENE - UCLA: PC1 > 0.03

This led to excluding these numbers of individuals: SGENE - Bonn (1 control), Cardiff UK (10 cases, 96 controls), SGENE - Copenhagen (11 cases, 9 controls), SGENE - Munich (32 cases, 3 controls), SGENE - TOP3 (11 cases, 1 control), SGENE - UCLA (1 case, 1 control).

The analysis showed GC  $\lambda=1.23$  ( $\lambda_{1000}=1.02$ ), compared with  $\lambda=1.24$  ( $\lambda_{1000}=1.02$ ) including these outliers. Across all SNPs, we observed a correlation of  $r^2 = 0.997$  (Pearson; Figure S9) between the analyses.

3b. We analyzed all single studies separately and performed an SE-weighted meta-analysis, including the mentioned PCs (1,2,3,4,6) as covariates, yielding  $\lambda=1.21$  and a correlation of  $r^2 = 0.992$  (Pearson; Figure S3) to the original scan. *P*-values in this analysis were calculated by summing Z scores with each dataset's Z score multiplied by the inverse of that dataset's standard error divided by the square root of the sum of the squared inverse standard errors. Combined ORs were calculated by summing log ORs with each log OR weighted by the inverse of its variance.

3c. We performed the stage1 analysis, including all 20 PCs as covariates, yielding  $\lambda=1.23$  ( $\lambda_{1000}=1.02$ ) with correlation  $r^2 = 0.996$  (Pearson) to original scan.

3d. As a most stringent analysis we created 10 PCs in each study separately on a higher number of LD pruned SNPs (~60K SNPs), allowing Eigenstrat<sup>56</sup> to exclude outliers based on 6 SE and performed association within each study, combining their results in a SE weighted form (see 8b. above). Even with this very stringent control for

population stratification, we obtained highly concordant results (Figure S2, Pearson correlation=0.935,  $\lambda=1.20$ )

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#### 4. Stage 2 Genotyping QC & Association Analyses (focused genotyping)

- **University of Queensland and Australian Schizophrenia Research Bank Stage 2 Replication Genotyping:** Forensic analysis was conducted on these DNA samples (N=1,540) using a panel of 12 simple tandem repeat (STR) markers (D12S78, D2S2211, D11S4151, D12S345, D2S337, D14S283, D11S904, D8S284, D2S125, DXS1227, DXS993, DYS19). Gender checking was performed using X-linked (2) and Y-linked (1) STRs. Gender was assigned to 132 individuals with no previously recorded gender. The gender of 19 individuals was re-assigned given definitive genotype data, while the gender of another 23 individuals was assigned “unknown” because of inconsistency with the genetic data (that was not definitive). The focused SNP genotyping (platform: Sequenom MassArray with MALDI-TOF-based mass spectrometry; chemistry: Sequenom iPLEX) completion rate for the association analyses was 97.9%.
- **University of Queensland and Australian Schizophrenia Research Bank Stage 2 Association Analysis:** The likelihood of higher-order relatives in the dataset was investigated using RELPAIR 2.0.1<sup>57</sup>. We accounted for genotyping error (0.01) and considered all pairs with LOD of  $\geq 5$  (likelihood of inferred relationship divided by the likelihood of no relationship) to be true relatives. There were 26 such pairs (N=12 parent-offspring, N=10 full siblings, N=4 putative monozygotic twin pairs), including one nuclear family (2 parents, 2 offspring) and one set of 3 full siblings. We removed a total of 23 individuals from the dataset to eliminate this family structure. An additional two individuals completely failed replication genotyping and were removed.
- **SGENE Stage 2 Replication Genotyping:** The genome-wide typed samples from England, Finland (Helsinki and Kuusamo), Germany (Munich), Italy, and Iceland (deCODE) were part of the initial SGENE study, and were typed at deCODE Genetics using the Illumina HumanHap300 BeadChip. The Danish (Aarhus) genome-wide typed sample was typed at AROS Applied Biotechnology A/S and Aarhus University using the Illumina HumanHap610 BeadChip. Only samples with a call-rate greater than 98% were included in the analysis. For all SNPs presented, SNP yield was greater than 98% for both cases and controls, with control Hardy-Weinberg equilibrium  $p > 0.001$ .
- With the exception of the Belgium control samples, which were typed using the Illumina HumanHap300 chip, the follow-up samples (focused genotyping replication samples) were typed at deCODE Genetics using Centaurus assays (Nanogen). Centaurus assay quality was evaluated by genotyping the CEU HapMap samples and comparing the results with the publicly released HapMap data. Assays with a greater than 1.5% mismatch rate were not used. Only samples with yield greater than 90% were included. For all SNPs presented, SNP yield was greater than 95% for both cases and controls, with control Hardy-Weinberg equilibrium  $p > 0.01$ .
- **SGENE Stage 2 Replication Association Analysis:** Association analysis was carried out using a likelihood procedure described previously<sup>58</sup>. Genomic control<sup>59</sup> was used to correct for relatedness and potential population stratification in each genome-wide typed study group. The Illumina HumanHap300 typed study groups and the follow-up groups were combined using the Mantel-Haenszel model<sup>60</sup>. Those two groups and the Danish (Aarhus)



genome-wide typed group were joined using summary statistics. *P*-values were calculated by summing Z scores with each dataset's Z score multiplied by the inverse of that data set's standard error divided by the square root of the sum of the squared inverse standard errors. Combined ORs were calculated by summing log ORs with each log OR weighted by the inverse of its variance.

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## 5. Score analysis to test a polygenic model of inheritance

We have used the GWAS mega-analysis sample (Stage 1) to carry out an additional test of the score analysis method described by the International Schizophrenia Consortium (ISC) in detail in their Supplementary Information file <sup>13</sup>. The ISC used this method to test if aggregate effects of common SNPs could be replicated across GWAS datasets, and interpreted their results as supporting the hypothesis that many common SNPs with small effects on risk contribute to schizophrenia risk (polygenic inheritance).

Briefly, this method involves using the association test results (log of the odds ratio) for each of a set of SNPs from a training dataset to form quantitative scores whose ability to predict case-control status in a test dataset is then evaluated:

- (1) Common SNPs in approximate linkage equilibrium were selected. In the ISC report, ~74,000 SNPs were selected which had MAF>2%, high call rate (>0.99) and had no pairwise  $r^2$  value (LD) >0.25 in any 200-SNP sliding window. Here, because our Stage 1 GWAS were performed on diverse genotyping platforms, we decided to perform analyses in a slightly altered procedure: we also used only SNPs with MAF>2%, then we restricted to SNPs with very high imputation quality (info R2 score >0.9). This SNP set underwent a *p*-value informed LD clumping procedure with the above parameters (pairwise  $R^2$  <0.25, 200 SNP window). As opposed to the *p*-value blind LD pruning procedure from the ISC, we could here examine SNP groups with far lower *p*-values. Because of the complicated LD structure and the widespread association signal in the MHC, we decided to exclude this region (chr.6, 25Mb-35Mb) and we were left with 117K LD independent SNPs.
- (2) In the training dataset, association tests are computed for each SNP (correcting for ancestry-based covariates) and expressed as the log of the odds ratio for a test allele.
- (3) Several sets of quantitative scores are then computed for each case and control in the test dataset, based on the pT (*p*-value threshold) proportion of SNPs with *p*-values in the training dataset -- here, we varied pT from 0.0001 to 1.0.
- (4) For each set of SNPs as defined by pT, the score for each subject in the test dataset is computed as the sum (across all selected SNPs) of the individual's dosage of the test allele multiplied by the training dataset log(OR) for that allele.
- (5) For each SNP set two outcome variables are reported: 1) The significance of the case-control score difference was analyzed by standard logistic regression in  $R^{61}$ , including ancestry based principal component scores and a study indicator as covariates. 2) The proportion of variance explained ( $R^2$ ) was computed by subtracting the Nagelkerke's  $R^2$  attributable to ancestry covariates alone from the  $R^2$  for polygenic scores plus covariates. The latter analysis required the package Design<sup>62</sup>.



The rationale for this approach is that it is possible that many SNPs make small contributions to risk, with ORs ranging from those which are detectable in very large samples (e.g., ~1.1 as reported for schizophrenia in our mega-analysis) to very small ORs which could not be detected singly in any feasible sample. Thus, some of these latter SNPs would produce very small ORs in the training dataset, but all of these SNPs would contribute to the ability of the quantitative score to predict risk in other datasets.

In the ISC report, the ISC sample was used as the training dataset, and the MGS and Cardiff samples as test datasets.  $P$ -values for prediction of disease status were  $2 \times 10^{-28}$  in the MGS sample and  $5 \times 10^{-11}$  in the smaller Cardiff sample, with approximately 2.3-3% of the variance explained. The ISC supplementary file reported simulation studies demonstrating that the observed patterns of results for schizophrenia were consistent only with results from models that included large numbers of common SNPs each with very small effects on risk, with the models differing primarily in the distribution of these effects across those SNPs. A range of models for multiple rare variants did not produce results consistent with the actual data. Numerous sources of possible confounders were studied, and it was concluded that the observed results were most likely due to a polygenic contribution of multiple common SNPs, each with small effects, to schizophrenia risk.

Here we report on a new score analysis in which the ISC, MGS, and Cardiff samples were combined into a training dataset, and all other Stage 1 samples were combined into a test dataset. Thus, we attempted to predict disease status in a test dataset that was completely independent of the ones used in the ISC paper. We hypothesized that because the training dataset was now more than twice as large as the ISC sample alone, a larger proportion of variance would be explained. Thus, for comparison we also repeated the two analyses reported previously by ISC, using the ISC as a training dataset to predict disease status first in the MGS and then in the Cardiff datasets, but using all imputed SNPs in the analyses. As in the Stage 1 mega-analysis, duplicate and related DNA specimens were excluded.

In the first two analyses, we used the ISC dataset as the training dataset, consisting of 3,307 cases and 3,553 controls. The first target dataset (MGS) contained 2,679 cases and 2,484 controls. The second target dataset (Cardiff) contained 472 cases and 2,934 controls. These ID numbers differ slightly from the original publications by these studies because new quality control analyses were performed on all PGC datasets as described above.

In the third experiment we combined ISC with MGS and Cardiff as the training dataset. This resulted in 6,458 cases and 8,971 controls. As the target dataset we used individuals from all other datasets within the Stage 1 GWAS (2,936 cases and 3,492 controls), including SGENE - Bonn, CATIE, SGENE - Copenhagen, SGENE - Munich, SGENE - TOP3, SGENE - UCLA, and Zucker - Hillside. For each individual in the target sample, we weighted its individual post-imputation dosage by the log odds ratio from the discovery sample, building SNP collections with  $p$ -value thresholds of  $p < 0.0001$ ,  $p < 0.001$ ,  $p < 0.01$ ,  $p < 0.05$ ,  $p < 0.1$ ,  $p < 0.2$ ,  $p < 0.3$ ,  $p < 0.4$ ,  $p < 0.5$ , and  $p \leq 1.0$  (i.e., all SNPs).

We used PLINK's `--score` function to calculate scores, described at this URL: [pengu.mgh.harvard.edu/~purcell/plink/profile.shtml](http://pengu.mgh.harvard.edu/~purcell/plink/profile.shtml). To account for population stratification, the training analysis was performed in the usual logistic regression framework, including study indicator and significant multi-dimensional scaling (MDS) scores. In the target sample, we estimated the variance explained in disease state by the difference in the Nagelkerke pseudo  $r^2$  of an analysis including the score and covariates such as site and ancestry principal component scores vs. an analysis with the covariates alone.

Table S9 shows  $R^2$  values for each of the three analyses for each pT value. We could show  $R^2$  estimates up to 5.8% and  $p$ -values down to  $6.2 \times 10^{-65}$ .  $R^2$  estimates do not show the direction of the effect, but here, all effects are in the predicted direction (i.e., quantitative scores predict increased risk of disease). Thus as predicted, the new analysis, with a much larger training dataset, explained a larger proportion of the variance in disease status in a test dataset that was completely independent of the datasets used in the original ISC report. All values are depicted in Figure S6.

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Shore – Long Island Jewish Health System, and grants from National Alliance for Research on Schizophrenia and Depression (to AKM), and the National Institutes of Health (K23MH001760 and R01MH079800 to AKM; R01MH0084098 to TL; and Center grants P30MH074543 to John M. Kane and M01RR018535 to Kevin J. Tracey).

**Stage 2: Replication follow-up – European ancestry sample 1 – Multicenter-Pedigree.** We thank the many family members who participated in the studies that recruited these samples. National Institute of Mental Health (NIMH) grants 7R01MH062276 (DFL, CL, MJO, and DBW), 5R01MH068922 (PVG), 5R01MH068921 (AEP) and 5R01MH068881 (BPR) supported this work. For the NIMH sample, data and biomaterials were collected in three projects that participated in the National Institute of Mental Health (NIMH) Schizophrenia Genetics Initiative. From 1991 to 1997, the principal investigators and co-investigators were: Harvard University, Boston, MA, U01 MH46318, MT Tsuang, SV Faraone, and J Pepple; Washington University, St Louis, MO, U01 MH46276, CR Cloninger, T Reich, and DM Svrakic; Columbia University, New York, NY U01 MH46289, CA Kaufmann, D Malaspina, and JM Harkavy-Friedman. The Center for Inherited Disease Research (CIDR) provided genotyping services, and is fully funded through a federal contract (N01-HG-65403) from the National Institutes of Health to The Johns Hopkins University. The NIMH DNA and Cell Repository at Rutgers University (DA Fugman, JA Tischfield) and the NIMH Center for Collaborative Genetic Studies on Mental Disorders (JP Rice) made infrastructure-related contributions to this project. We acknowledge the contributions of RR Crowe.

**Combined acknowledgements for: Stage 2: Replication follow-up – European ancestry sample 2 – SGENE – Aarhus and Stage 2: Replication follow-up – European ancestry sample 3 – SGENE – Aarhus.** This work was supported by grants from the Danish Council for Strategic Research (grant no. 2101-07-0059), H. Lundbeck A/S, The Faculty of Health Sciences at Aarhus University, and The Stanley Medical Research Institute.

**Stage 2: Replication follow-up – European ancestry sample 4 – SGENE – Belgium.** None listed.

**Stage 2: Replication follow-up – European ancestry sample 6 – SGENE – Iceland.** Genotyping of the SGENE samples was supported by the European Union (LSHM-CT-2006-037761 [Project SGENE], PIAP-GA-2008-218251 [Project PsychGene], and HEALTH-F2-2009-223423 [Project PsychCNVs]).

**Stage 2: Replication follow-up – European ancestry sample 7 – SGENE – England.** This work was supported by grants from the European Union (LSHM-CT-2006-037761/Project SGENE and HEALTH-F2-2009-223423/Project PsychCNVs).

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**Stage 2: Replication follow-up – European ancestry sample 9 – SGENE – Hungary.** None listed.

**Stage 2: Replication follow-up – European ancestry sample 10 – SGENE – Italy.**

This work was supported by a grant from the European Union: LSHM-CT-2006-037761/Project SGENE.

**Stage 2: Replication follow-up – European ancestry sample 14 – SGENE – Russia.**

This work was supported by a grant from the European Union (HEALTH-F2-2009-223423/Project PsychCNVs).

**Stage 2: Replication follow-up – European ancestry sample 15 – SGENE –**

**Sweden.** This work was supported from the Swedish Research Council (2006-2992, 2006-986, 2008-2167), the regional agreement on medical training and clinical research between Stockholm County Council and the Karolinska Institutet, Wallenberg Foundation, and the HUBIN project.

**Stage 2: Replication follow-up – European ancestry sample 18 – University of Queensland and Australian Schizophrenia Research Bank.** B.J.M., V.J.C., R.J.S., S.V.C., F.A.H., A.V.J., C.M.L., P.T.M., C.P., and U.S. were supported by the Australian Schizophrenia Research Bank, which is supported by an Enabling Grant from the National Health and Medical Research Council (Australia) [No. 386500], the Pratt Foundation, Ramsay Health Care, the Viertel Charitable Foundation and the Schizophrenia Research Institute and the NSW Department of Health. The Brisbane Psychosis Study (B.J.M., J.J.M., D.E.M.) was supported by an Australian Commonwealth Department of Health and Aging grant, and the Queensland Department of Health. M.A.B. is supported by a Principal Research Fellowship from the National Health and Medical Research Council (Australia). P.A.D. is supported by a University of Queensland Postdoctoral Research Fellowship (Australia). C.P. is supported by a Senior Principal Research Fellowship from the National Health and Medical Research Council (Australia). We acknowledge the help of: Linda Bradbury, Susette Cardy, David Chandler, Janell Collins-Langworthy, Trish Collinson, Cheryl Filippich, Jacob Gratten, David Hawkes, Danielle Lowe, Kathryn McCabe, Tamara MacDonald, Barry Maher, Marc Seal, Heather Smith, Melissa Tooney, Paul Tooney, and Melinda Ziino.

**Stage 2: Replication follow-up – European ancestry sample 19 Irish Schizophrenia Genomics Consortium (ISGC for cases) and Wellcome Trust Case Control Consortium 2 (WTCCC2 for controls).** **For the ISGC**, we additionally acknowledge the contributions of individuals from The Health Research Board, Dublin, Ireland (Dermot Walsh) and the Neuropsychiatric Genetics Research Group, Department of Psychiatry and Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland (William Gilks, John L. Waddington, Colm McDonald, Eadbhard O'Callaghan, Kieran Murphy, and Ted Dinan). **For the WTCCC2**, funding for this study was provided by the Wellcome Trust, as part of the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z). We acknowledge use of the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02, and of the UK National Blood Service controls funded by the Wellcome Trust. The Irish Schizophrenia Genomics Consortium (ISGC) members have been funded by the Wellcome Trust, Science Foundation Ireland, the Health Research Board, and the National Institute of Mental Health. We thank all subjects and mental health facilities who participated in recruitment for this project. We thank the Irish Blood Transfusion Service (IBTS) and its donors for their involvement. **For the WTCCC2**, we additionally acknowledge the individuals from Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford, England, United Kingdom (Anna Rautanen\*, Céline Bellenguez†, Colin Freeman†); Department of Statistics, University of Oxford, Oxford, England, United Kingdom (Daniel Davison†); Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, England, United Kingdom (Leena Peltonen\*‡, Panos Deloukas\*‡, Jeffrey C.



Barrett†, Cordelia Langford‡, Sarah E. Hunt‡, Sarah Edkins‡, Rhian Gwilliam‡, Hannah Blackburn‡, Suzannah J. Bumpstead‡, Serge Dronov‡, Matthew Gillman‡, Emma Gray‡, Naomi Hammond‡, Alagurevathi Jayakumar‡, Owen T. McCann‡, Jennifer Liddle‡, Marc L. Perez‡, Simon C. Potter‡, Radhi Ravindrarajah‡, Michelle Ricketts‡, Matthew Waller‡, Paul Weston‡, Sara Widaa‡, Pamela Whittaker‡, Panos Deloukas\*, Antony P. Attwood¶, Willem H. Ouwehand); Genetics and Infection Laboratory, Cambridge Institute of Medical Research, Addenbrooke's Hospital, Cambridge, England, United Kingdom (Jenefer M. Blackwell\*§); Division of Psychological Medicine and Psychiatry, Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King's College London and The South London and Maudsley NHS Foundation Trust, Denmark Hill, London, England, United Kingdom (Elvira Bramon\*); University of Queensland Diamantina Institute, Princess Alexandra Hospital, University of Queensland, Brisbane, Queensland, Australia (Matthew A. Brown\*§); Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, England, United Kingdom (Juan P. Casas\*); Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland (Aiden Corvin\*§); Department of Psychological Medicine, Cardiff University School of Medicine, Heath Park, Cardiff, Wales, United Kingdom (Nicholas Craddock\*); Molecular and Physiological Sciences, The Wellcome Trust, London, England, United Kingdom (Audrey Duncanson\*); Centre for Gastroenterology, Bart's and the London School of Medicine and Dentistry, London, England, United Kingdom (Janusz Jankowski\*); Clinical Neurosciences, St George's University of London, London, England, United Kingdom (Hugh S. Markus\*); Department of Medical and Molecular Genetics, King's College London School of Medicine, Guy's Hospital, London, England, United Kingdom (Christopher G. Mathew\*§, Richard C. Trembath\*); Oxford Centre for Diabetes, Endocrinology and Metabolism (ICDEM), Churchill Hospital, Oxford, England, United Kingdom (Mark I. McCarthy\*§); Biomedical Research Centre, Ninewells Hospital and Medical School, Dundee, Scotland, United Kingdom (Colin N. A. Palmer\*); Social, Genetic and Developmental Psychiatry Centre, King's College London Institute of Psychiatry, Denmark Hill, London, England, United Kingdom (Robert Plomin\*); University of Cambridge Department of Clinical Neurosciences, Addenbrooke's Hospital, Cambridge, England, United Kingdom (Stephen J. Sawcer\*); Department of Cardiovascular Science, University of Leicester, Glenfield Hospital, Leicester, England, United Kingdom (Nilesh Samani\*); Glaucoma Research Unit, Moorfields Eye Hospital NHS Foundation Trust, London, England, United Kingdom (Ananth C. Viswanathan\*); Department of Genetics, University College London Institute of Ophthalmology, London, England, United Kingdom (Ananth C. Viswanathan\*); Department of Molecular Neuroscience, Institute of Neurology, Queen Square, London, England, United Kingdom (Nicholas Wood\*); Department of Haematology, University of Cambridge and National Health Service Blood and Transplant, Long Road, Cambridge, England, United Kingdom (Antony P. Attwood¶, Jonathan Stephens¶, Jennifer Sambrook¶, Willem H. Ouwehand¶); ALSPAC DNA Bank, Department of Social Medicine, University of Bristol, Bristol, England, United Kingdom (Wendy L. McArdle£); ALSPAC Laboratory, Department of Social Medicine, Bristol, England, United Kingdom (Susan M. Ring£); and Division of Community Health Sciences, St George's Hospital, London, England, United Kingdom (David P. Strachan£) for their contributions to the WTCCC2 Management Committee (\*), Data and Analysis Group (†), DNA, Genotyping, Data QC and Informatics Group (§), Publications Committee (§), UK Blood Services Controls (¶), and 1958 Birth Cohort Controls (£).

### C. Competing Financial Interests

**Competing Financial Interests.** Eli Lilly funded portions of the genotyping for CATIE and TOP. Dr. Patrick F. Sullivan received research funding from Eli Lilly in connection with CATIE. Dr. T. Scott Stroup received research funding from Eli Lilly and consulting fees from Janssen Pharmaceutica, GlaxoSmithKline and Bristol-Myers Squibb. Dr. Jeffrey A Lieberman received research funding from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Pharmaceutica and Pfizer, and consulting and educational fees from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Novartis, Pfizer and Solvay. Dr. David St Clair received research funding from GlaxoSmithKline and Generation Scotland, Genetics Health Initiative. Dr. Farooq Amin has received funds from Pfizer, Organon, and the Foundation for the National Institutes of Health. Dr. Donald W. Black has received research support from Shire and Forest, has been on the speakers' bureau for Pfizer, and has received consulting honoraria from Forest and Jazz. Dr. Thomas Werge has received consulting and lecture fees from H. Lundbeck A/S. Dr. Ole A. Andreassen has received Speaker's honorarium from AstraZeneca, Janssen, BMS and GSK. Dr. Ingrid Melle has received Speaker's honorarium from Janssen and AstraZeneca. Dr. Anil K. Malhotra has received consulting fees or honoraria from Eli Lilly & Company, Janssen Pharmaceutica, Merck, Bristol-Meyers Squibb, Pfizer, PGxHealth (a division of Clinical Data, Inc.), Roche Diagnostics, and Vanda Pharmaceuticals, and has received research support from Eli Lilly & Company. Dr. Todd Lencz has received consulting fees or honoraria from Merck, Eli Lilly & Company, Golden Helix, Inc., InforMed Insights, and PGxHealth (a division of Clinical Data, Inc.). Dr. Bitter has been an advisory board member/consultant/lecturer for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, EGIS, Janssen, Lundbeck, Novartis, Pfizer, Richter and ScheringPlough and received a grant for an investigator initiated study from Lundbeck. Dr. John J. McGrath has received consulting and speaker's fees from Johnson and Johnson, Schering Plough and Eli Lilly. Dr. Christos Pantelis has received grant support from Janssen-Cilag, Eli Lilly, Hospira (Mayne), Astra Zeneca; provided consultancy to Janssen-Cilag, Eli Lilly, Hospira (Mayne), Astra Zeneca, Pfizer, Schering Plough; and undertaken investigator initiated studies supported by Eli Lilly, Hospira, Janssen Cilag and Astra Zeneca. The Denmark-Aarhus group (The GEMS Study, PIs: Dr. Anders D. Børghlum, Dr. Ole Mors, Dr. Preben B. Mortensen) received research funding from H. Lundbeck A/S. Dr. Erik G. Jönsson has served as an unpaid consultant for Eli-Lilly.

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## **D. Supplementary Figures**

The following supplementary figures are presented on the following pages, with the number of pages dedicated to each figure indicated:

**Figure S1: Quantile-Quantile Plot.** – 1 page

**Figure S2: Scatterplot of  $p$ -values from meta-analysis (including Eigenstrat outlier exclusion and within site PCA creation) vs. mega-analysis (including study indicators) on log-scale.** – 1 page

**Figure S3: Scatterplot of  $p$ -values from meta-analysis vs. mega-analysis (including study indicators) on log-scale.** – 1 page

**Figure S4: Manhattan Plot - Stage 1.** – 1 page

**Figure S5: Region and Forest Plots.** – 26 pages

**Figure S6: Polygenic Analysis.** – 1 page

**Figure S7: Overall Values of Stage 1 LD-friends.** – 1 page

**Figure S8: Principal-Components Analysis (PCA) Plots.** – 9 pages

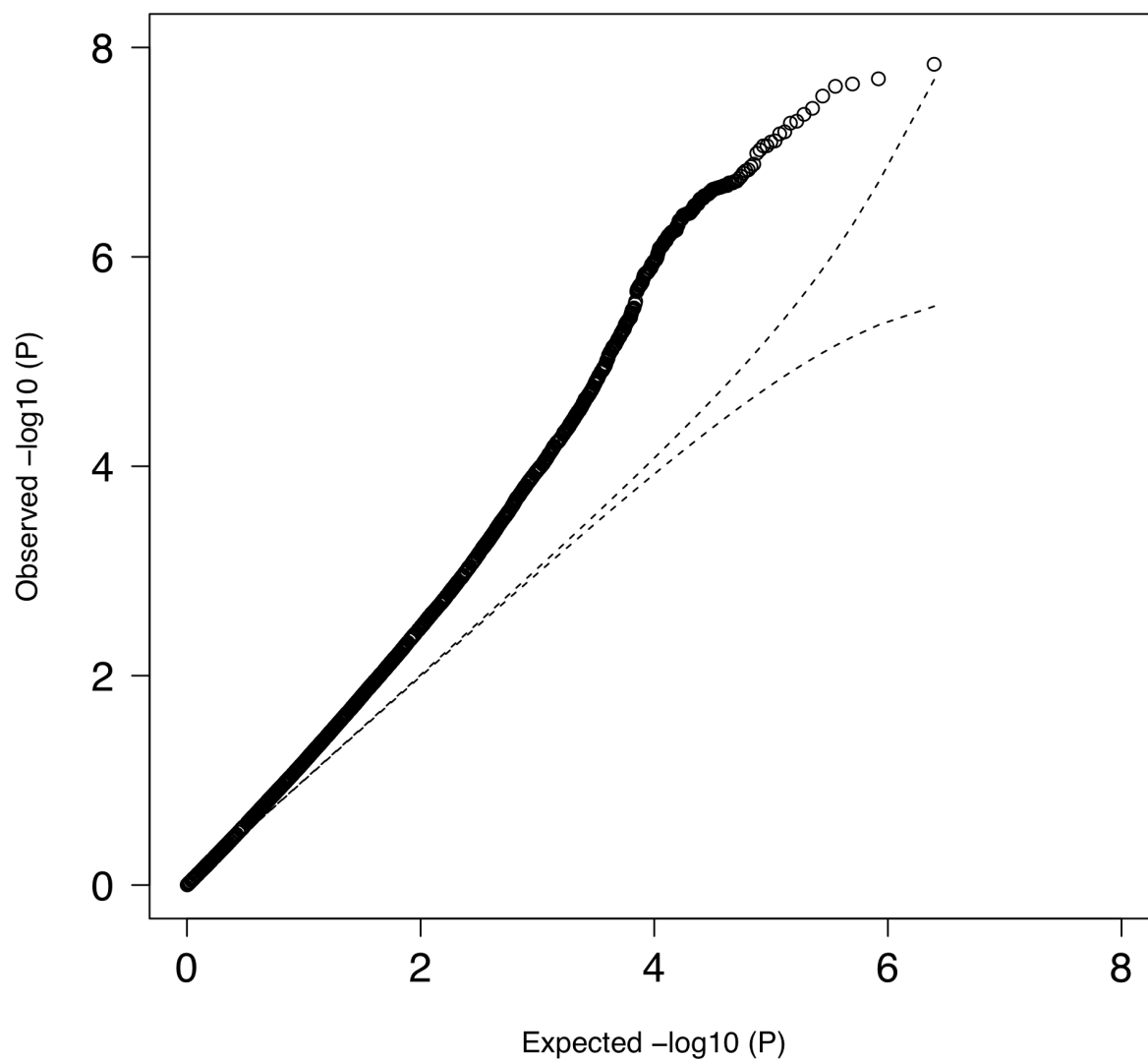
**Figure S9: Scatterplot of  $p$ -values from stricter outlier-exclusion vs. not, for mega-analysis (including study indicators) on log-scale.** – 1 page

**Figure S10: Quantile-Quantile Plots for Individual Stage 1 Samples.** – 5 pages

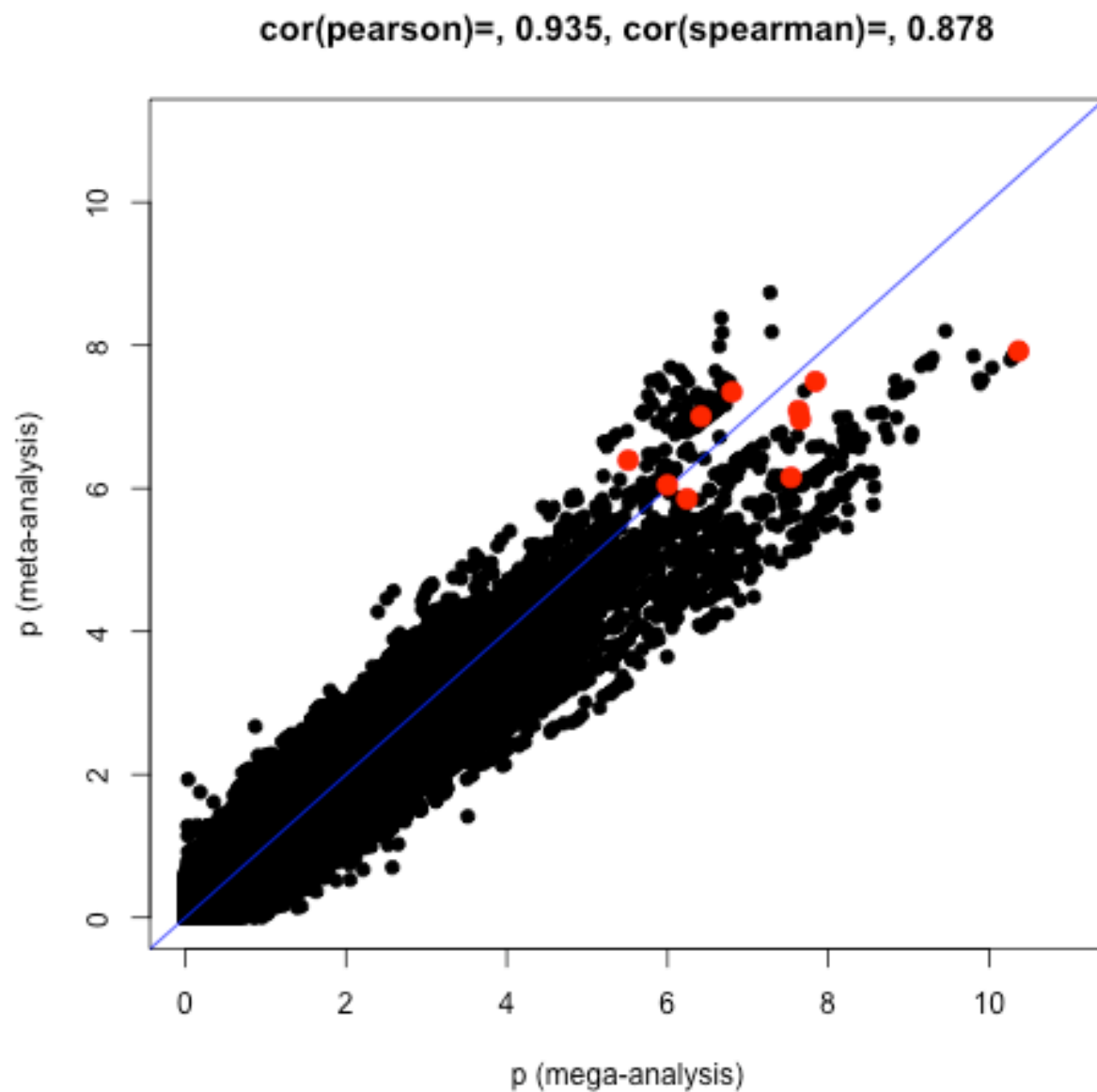
**Figure S11: Manhattan Plot - Stage 1 Individual Samples.** – 6 pages

**Figure S12: Multi-Dimensional Scaling for all Stage 1 Samples and HapMap3.** – 1 page

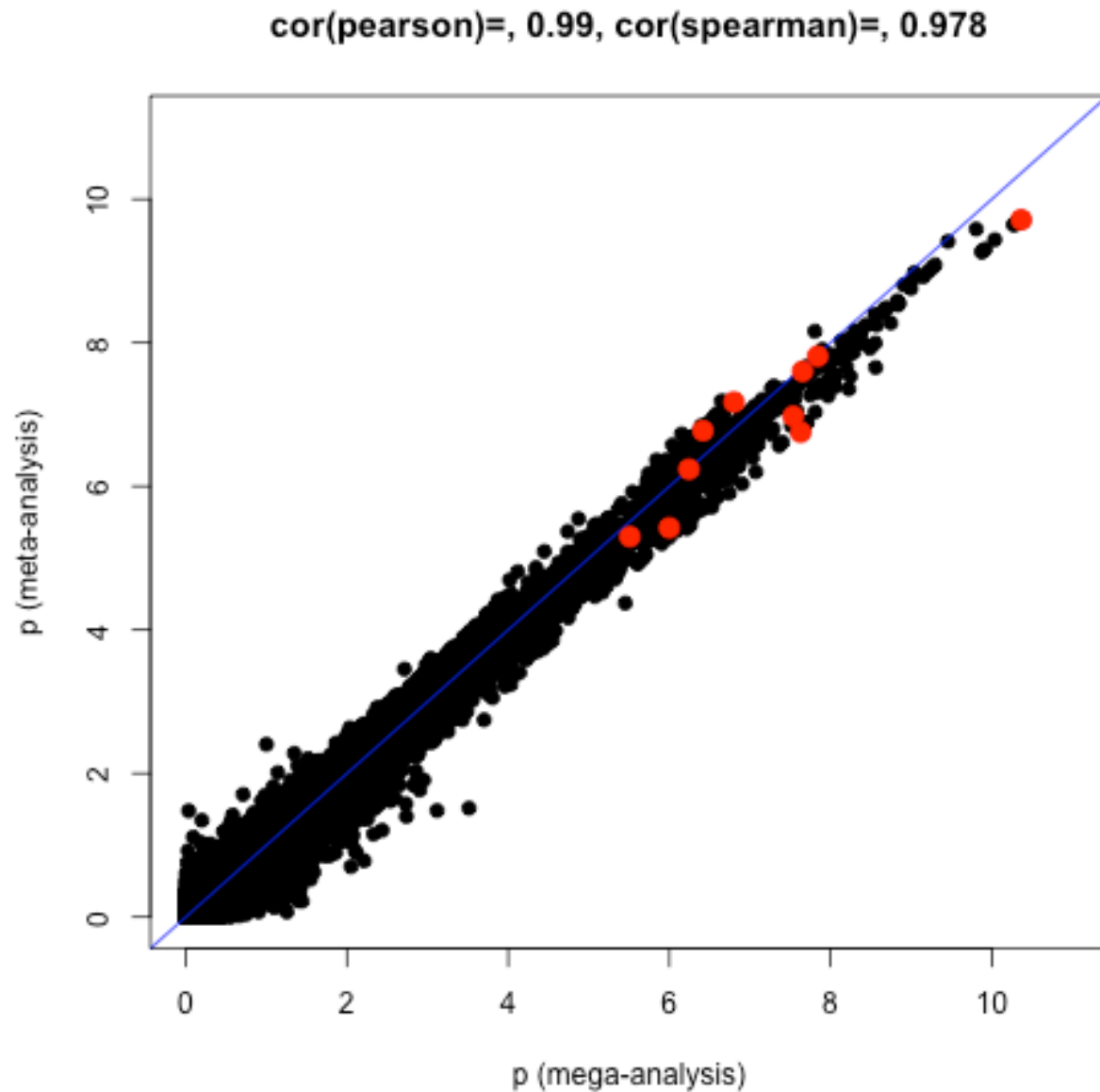
**Figure S1: Quantile-Quantile Plot.** The observed distribution of the  $-\log_{10}$  of nominal  $p$ -values (y-axis) demonstrates significant departure from the null (expected on x-axis).  $\lambda = 1.229$  ( $p$ -values  $N=1,252,901$ ), and  $\lambda_{1000}=1.021$  (9,394 cases and 12,462 controls). Individual Stage 1 sample QQ plots are in Figure S10.



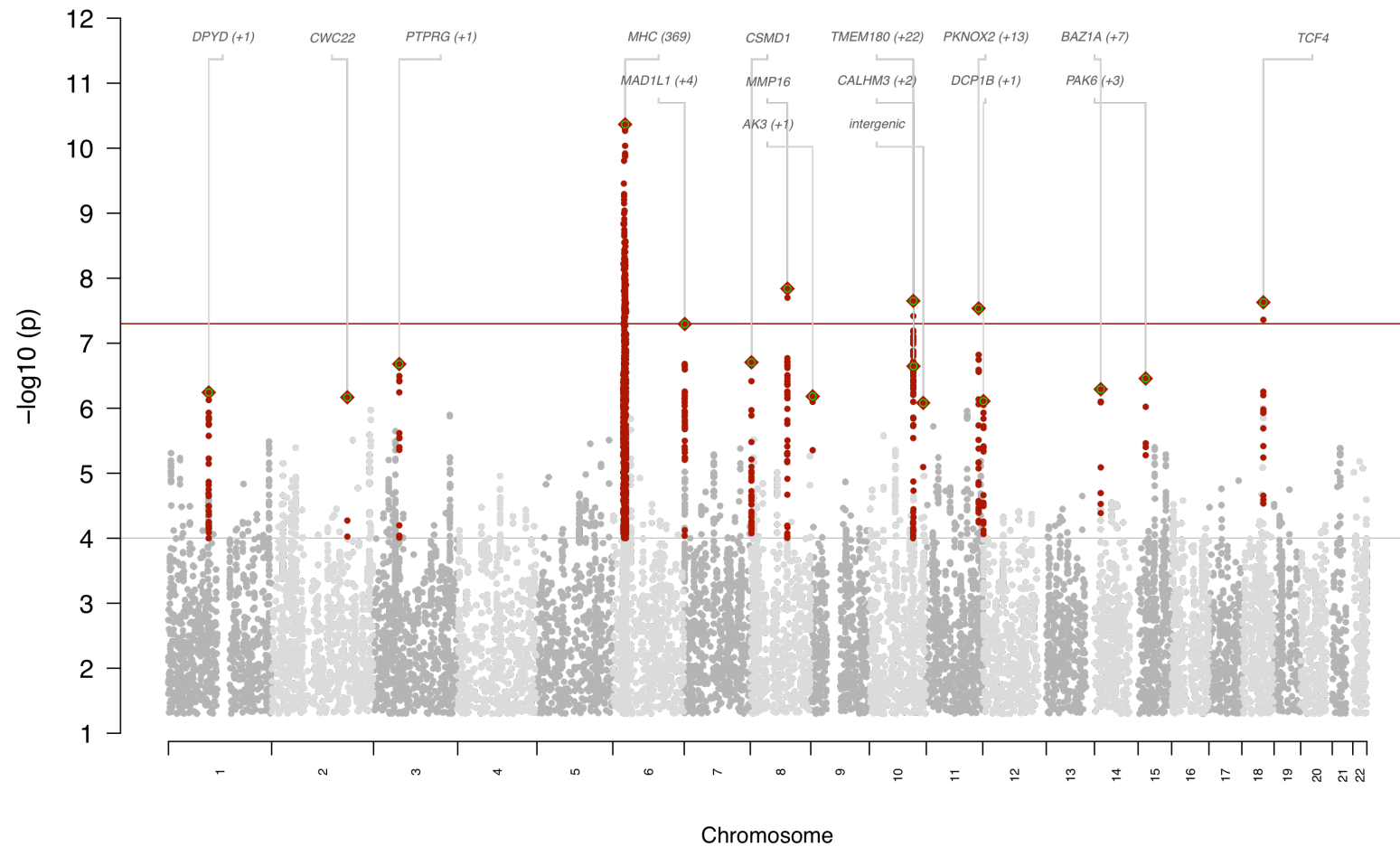
**Figure S2: Scatterplot of  $p$ -values from meta-analysis (including Eigenstrat outlier exclusion and within site PCA creation) vs. mega-analysis (including study indicators) on log-scale. Pearson's and Spearman's correlation coefficients are shown in the subtitle. SNPs from Table 2 are shown in red. See section A3d.**



**Figure S3: Scatterplot of  $p$ -values from meta-analysis vs. mega-analysis (including study indicators) on log-scale.** Pearson's and Spearman's correlation coefficients are shown in the subtitle. SNPs from Table 2 are shown in red. See section A3b.



**Figure S4: Manhattan Plot - Stage 1.** Standard  $-\log_{10}(p\text{-value})$  plot of the study results. Stage 1 results, 16 regions with one or more SNPs achieving  $p < 10^{-6}$  are highlighted in color (the most associated SNP with a big red diamond with an internal green circle, and its SNPs in LD ( $r^2 > 0.2$ ) with small red circles) and labeled with the name of the nearest gene. Individual Stage 1 sample Manhattan plots are in Figure S11.

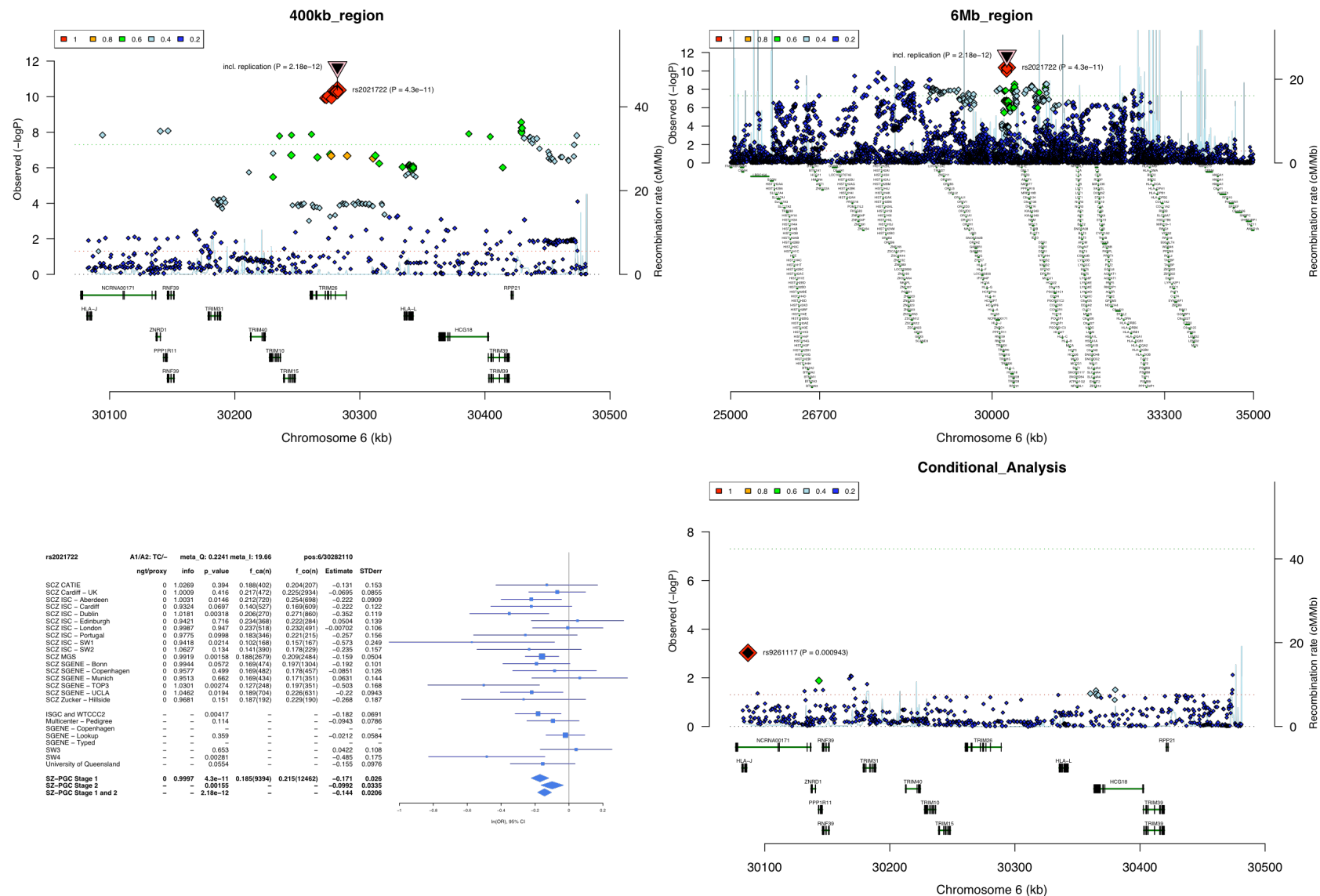




**Figure S5: Region and Forest Plots.** Regional  $p$ -value and forest plots for each of 26 genomic regions with one or more SNPs achieving a Stage 1  $p < 10^{-6}$  and/or a Combined Stages 1 & 2  $p < 10^{-6}$ . Each page displays the most associated SNP (key-SNP) and its genomic region from first column of Table 2 with four plots (from upper left to lower right): (1) Stage 1 scan results for each SNP  $\pm 200\text{kb}$  to key-SNP; x-axis: genomic position, y-axis:  $-\log_{10}(p\text{-value})$ ; larger SNP symbols are in higher LD (based on HapMap 3, HM3) to the key-SNP than smaller SNPs. Color-coding (from red to blue) denotes LD-information, see also legend within plot. (2) Same with  $\pm 3\text{Mb}$  range to key-SNP. (3) Forest-plot with scan results for each of the 17 individual Stage 1 samples, 8 Stage 2 samples or sample groups (SGENE – Lookup groups the remaining Stage 2 samples for which replication genotypes were looked up from GWAS results, and SGENE – Typed groups the remaining Stage 2 samples for which replication genotypes were from focused genotyping), and the full samples' (Stage 1, Stage 2, and Combined Stages 1 & 2) result for key-SNP. (4) same region as (2), analysis conditional on key-SNP, LD information (size and color) pointing to resulting best SNP in this region.  $\text{ngt} = 1$  for genotyped or 0 for imputed.  $\text{info} =$  imputation quality score (variance quotient).  $f_{\text{ca}}(n) =$  frequency in cases (number of cases).  $f_{\text{co}}(n) =$  frequency in controls (number of controls). Estimate =  $\ln(\text{OR})$ .  $\text{STDerr} =$  standard error of Estimate.

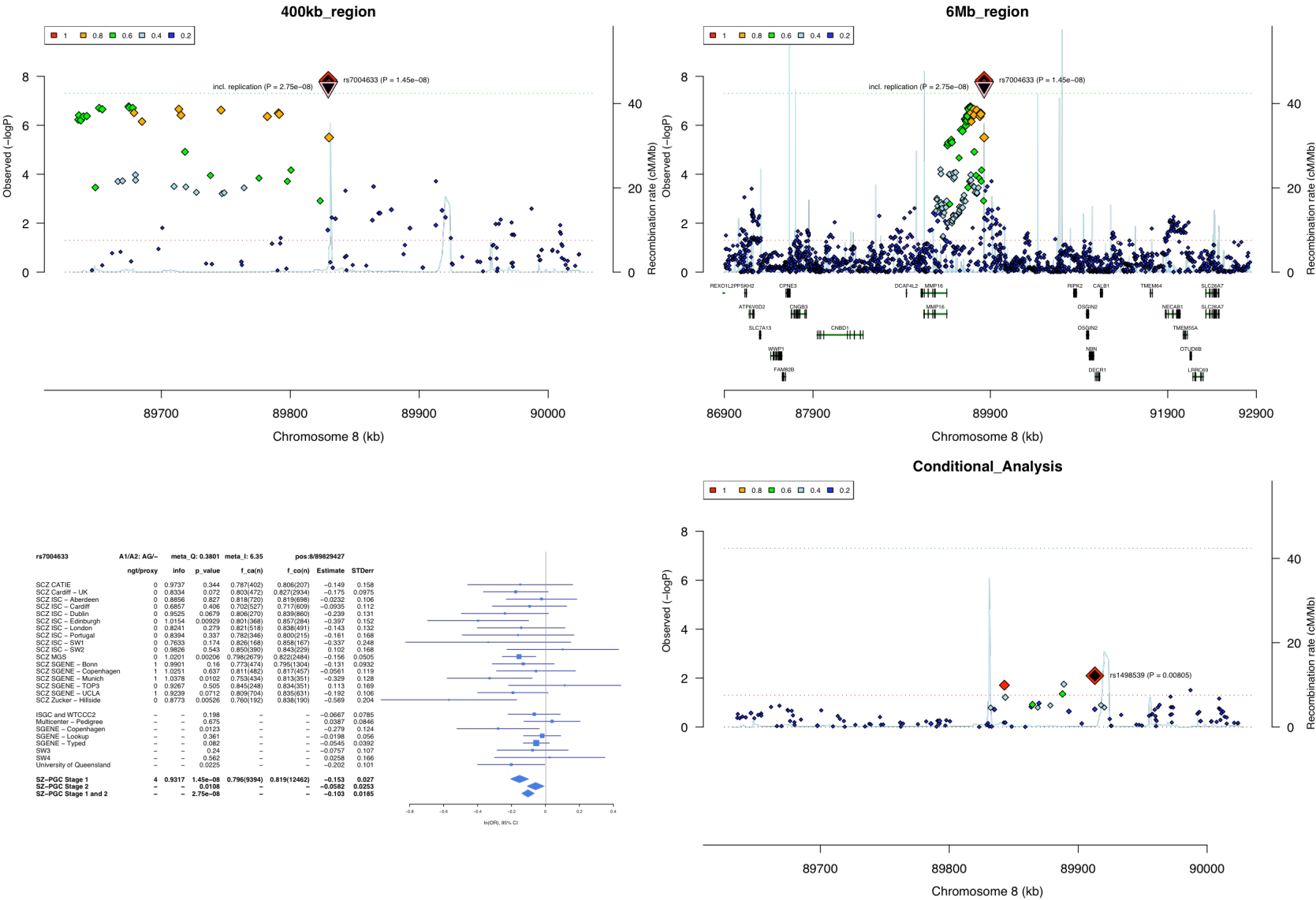
Each of the following pages has one of these 26 regions, with the key-SNP in the page title.

Figure S5: Region and Forest Plots – rs2021722.



SZ\_PGC, Supplementary Materials - S34

Figure S5: Region and Forest Plots – rs7004633.



SZ\_PGC, Supplementary Materials - S35

400kb\_region

Observed  $(-\log P)$

incl. replication ( $P = 1.11e-08$ )

rs11191580 ( $P = 2.23e-08$ )

CHN2

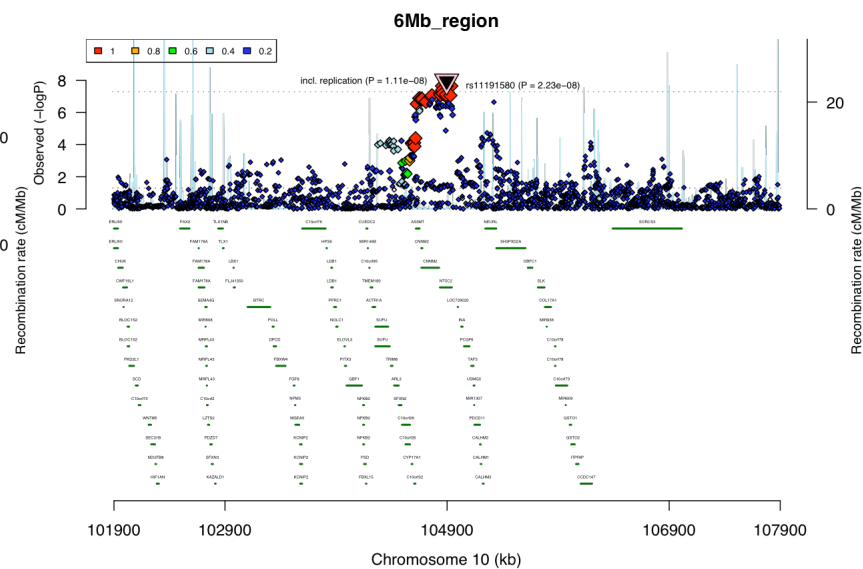
N7YC2

LOC729300

RAB

PRR43

Chromosome 10 (kb)



Nature Genetics: doi:10.1038/ng.940

**400kb\_region**

Observed  $-\log P$

Recombination rate (cM/Mb)

Chromosome 18 (kb)

**6Mb\_region**

Observed  $-\log P$

Recombination rate (cM/Mb)

Chromosome 18 (kb)

**Conditional\_Analysis**

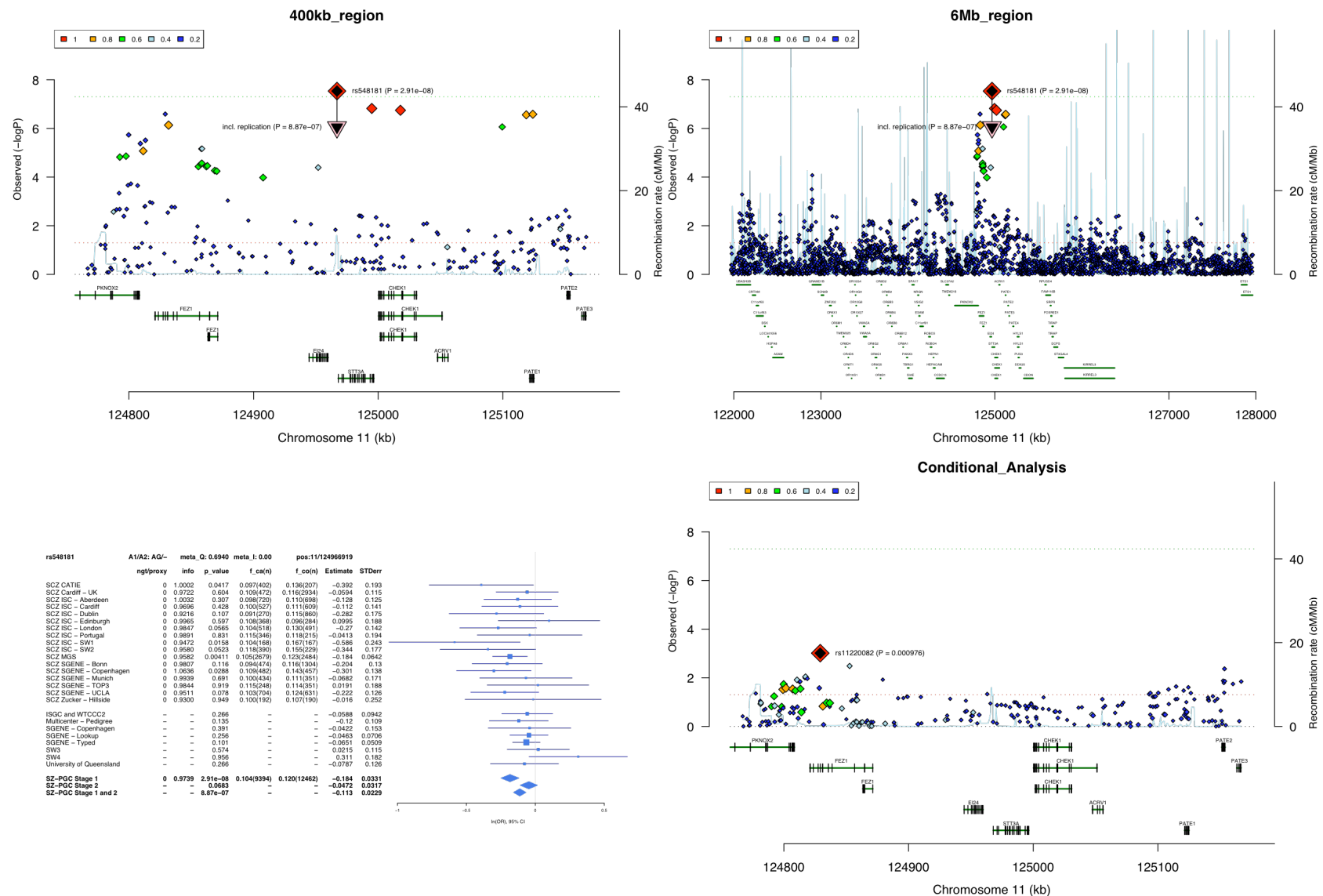
Observed  $-\log P$

Recombination rate (cM/Mb)

Chromosome 18 (kb)

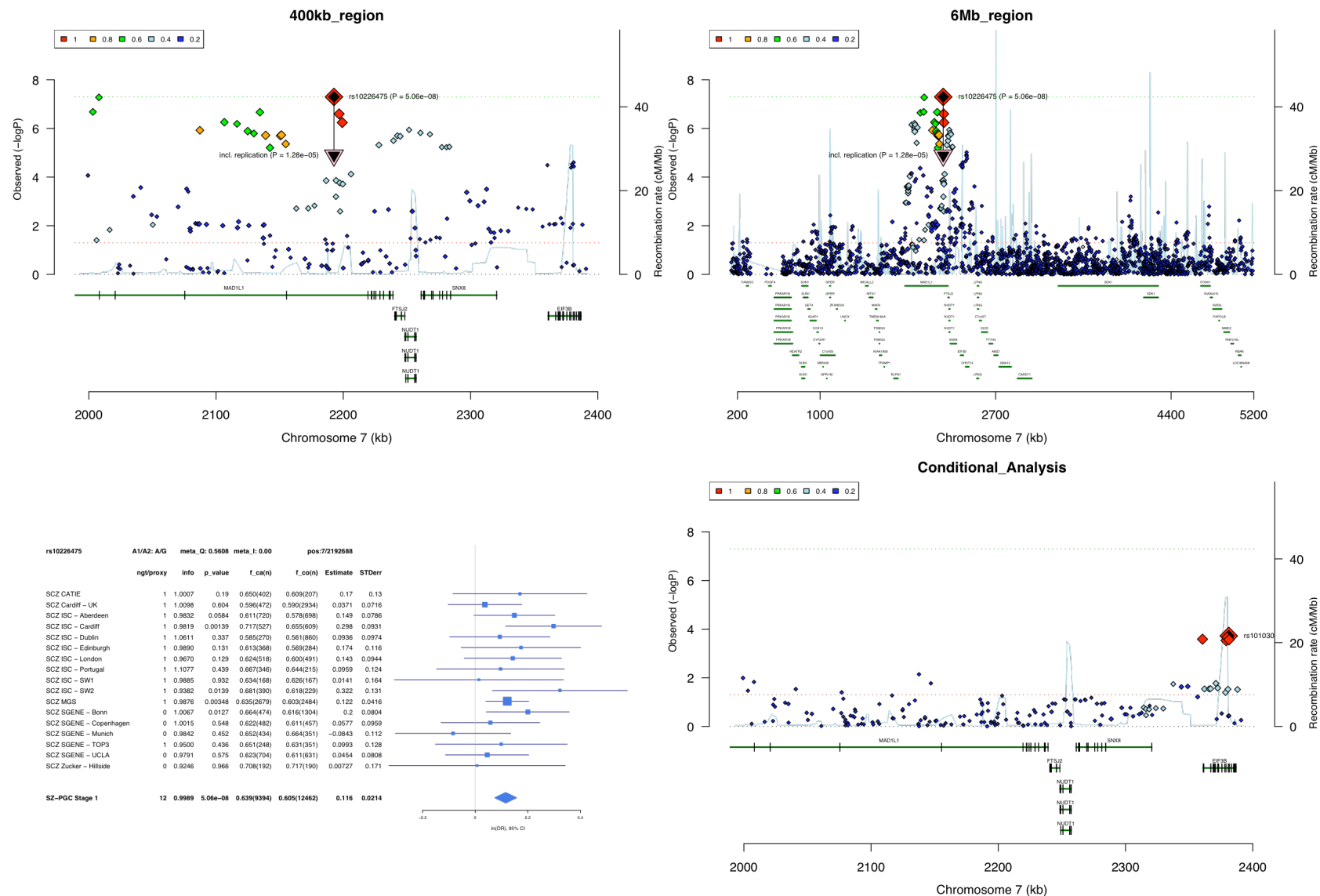
rs17512836	A1/A2: T/C	meta_Q: 0.4542	meta_I: 0.00	pos:18/51345959				
		ngtproxy	info	p_value	f_ca(n)	f_co(n)	Estimate	STDerr
SCZ CATIE	0	0.9476	0.244	0.964(402)	0.978(207)	-0.468	0.402	
SCZ Cardiff - UK	0	0.9934	0.171	0.970(472)	0.976(2934)	-0.288	0.21	
SCZ ISC - Aberdeen	0	0.9772	0.182	0.967(720)	0.977(698)	-0.317	0.238	
SCZ ISC - Cardiff	0	1.0223	0.225	0.968(527)	0.978(609)	-0.319	0.263	
SCZ ISC - Dublin	0	0.9557	0.97	0.983(270)	0.983(860)	-0.0145	0.391	
SCZ ISC - Edinburgh	0	1.1065	0.0158	0.969(368)	0.991(284)	-1.21	0.499	
SCZ ISC - London	0	0.9595	0.349	0.968(518)	0.973(491)	-0.256	0.273	
SCZ ISC - Portugal	0	0.9670	0.101	0.928(346)	0.950(215)	-0.45	0.275	
SCZ ISC - SW1	0	0.8817	0.305	0.977(168)	0.987(167)	-0.661	0.645	
SCZ ISC - SW2	0	1.0270	0.0594	0.969(390)	0.987(229)	-0.866	0.459	
SCZ MGS	0	0.9680	0.0128	0.963(2679)	0.972(2484)	-0.287	0.115	
SCZ SGENE - Bonn	0	0.9725	0.0122	0.958(474)	0.975(1304)	-0.525	0.209	
SCZ SGENE - Copenhagen	0	0.9570	0.332	0.978(482)	0.982(457)	-0.219	0.341	
SCZ SGENE - Munich	0	0.9779	0.0419	0.955(434)	0.972(351)	-0.258	0.294	
SCZ SGENE - TOP3	0	0.9653	0.0612	0.974(248)	0.990(351)	-0.902	0.482	
SCZ SGENE - UCLA	0	0.9853	0.948	0.961(704)	0.960(631)	0.0136	0.201	
SCZ Zucker - Hillside	0	0.8405	0.14	0.989(192)	0.975(190)	0.98	0.664	
SZ-PGC Stage 1	0	0.9815	2.35e-08	0.964(9394)	0.975(12462)	-0.341	0.0611	

Figure S5: Region and Forest Plots – rs548181.



SZ\_PGC, Supplementary Materials - S38

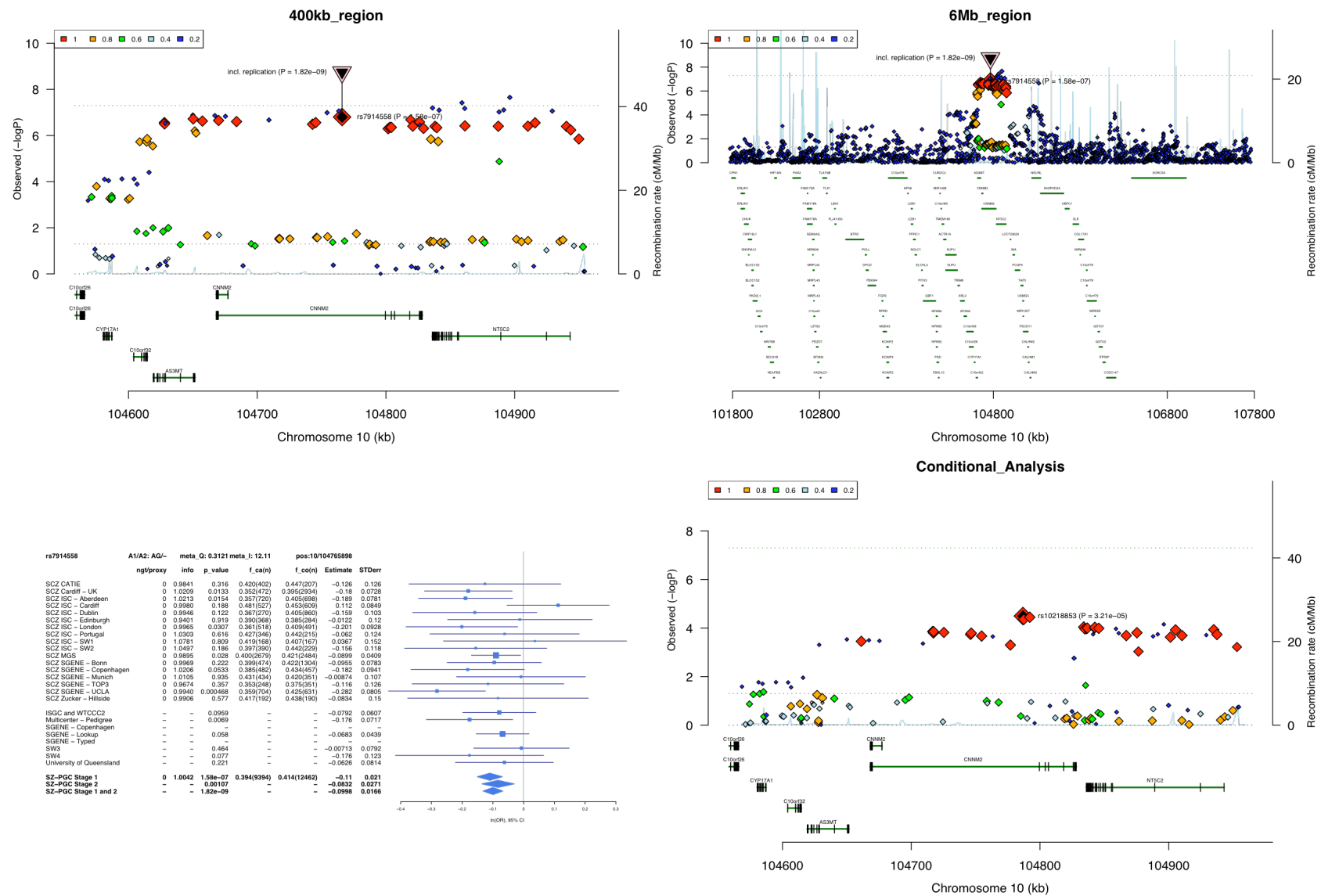
Figure S5: Region and Forest Plots – rs10226475.



SZ\_PGC, Supplementary Materials - S39

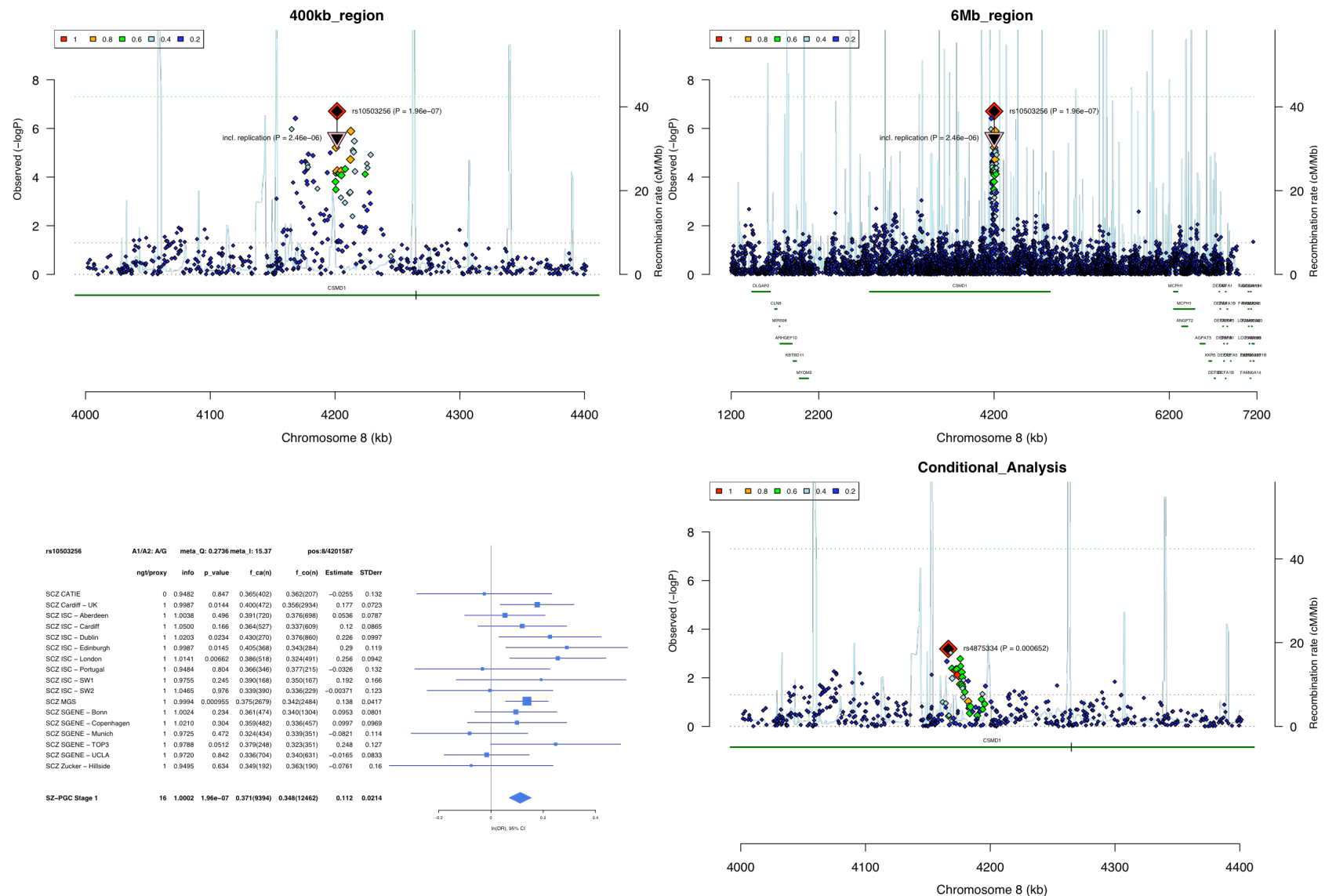


Figure S5: Region and Forest Plots – rs7914558.



SZ\_PGC, Supplementary Materials - S40

Figure S5: Region and Forest Plots – rs10503256.



SZ\_PGC, Supplementary Materials - S41

Figure S5: Region and Forest Plots – rs11130874.

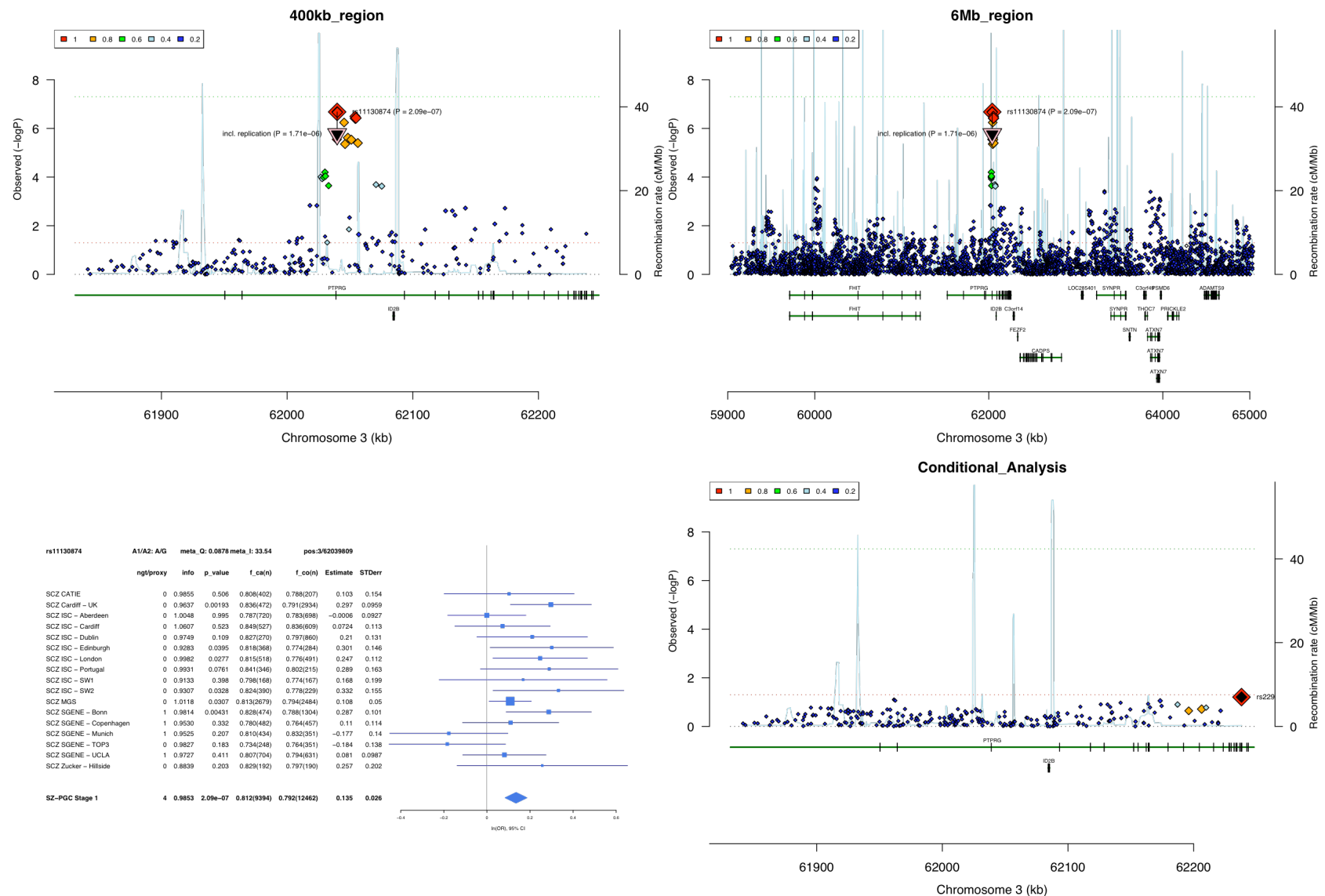
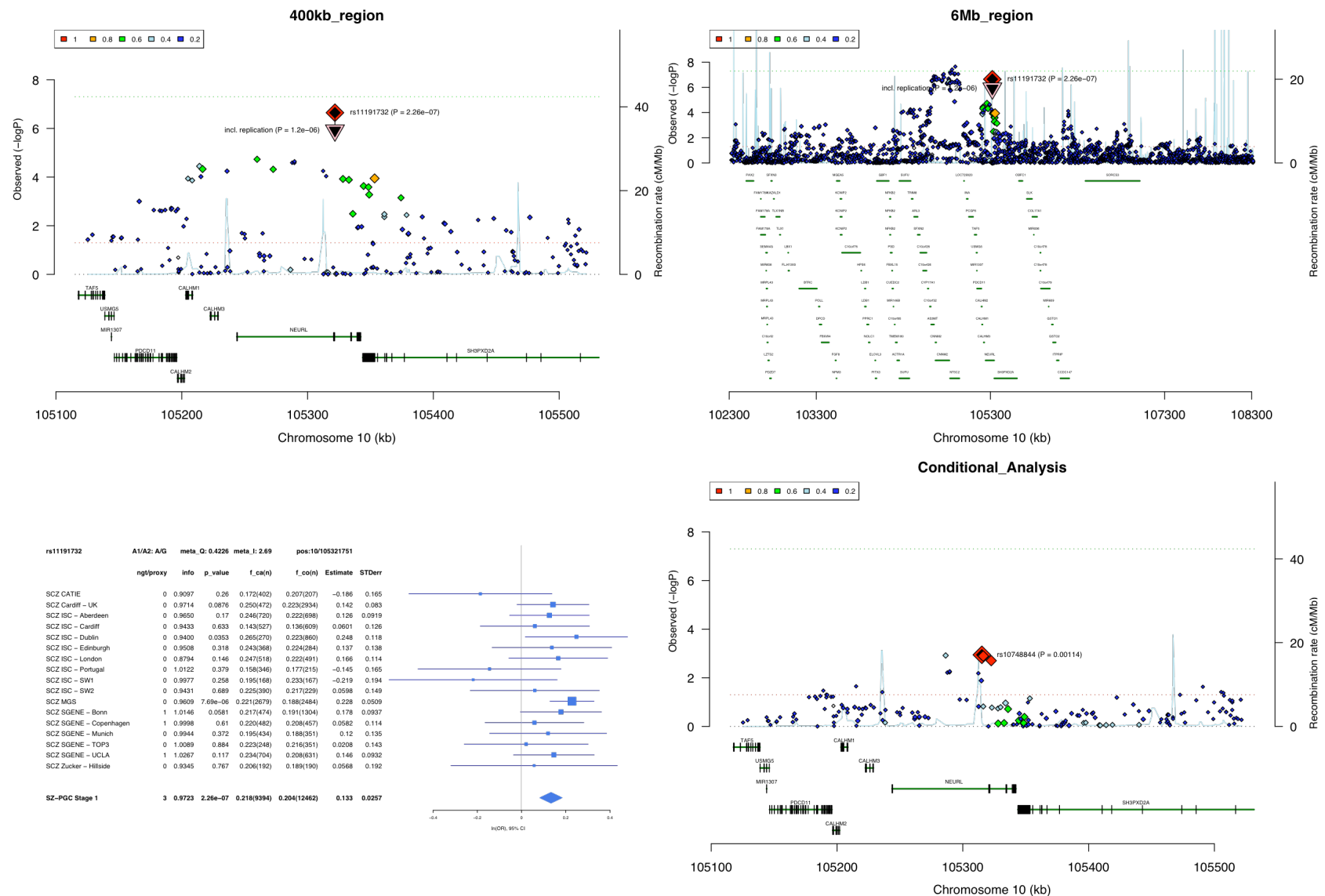
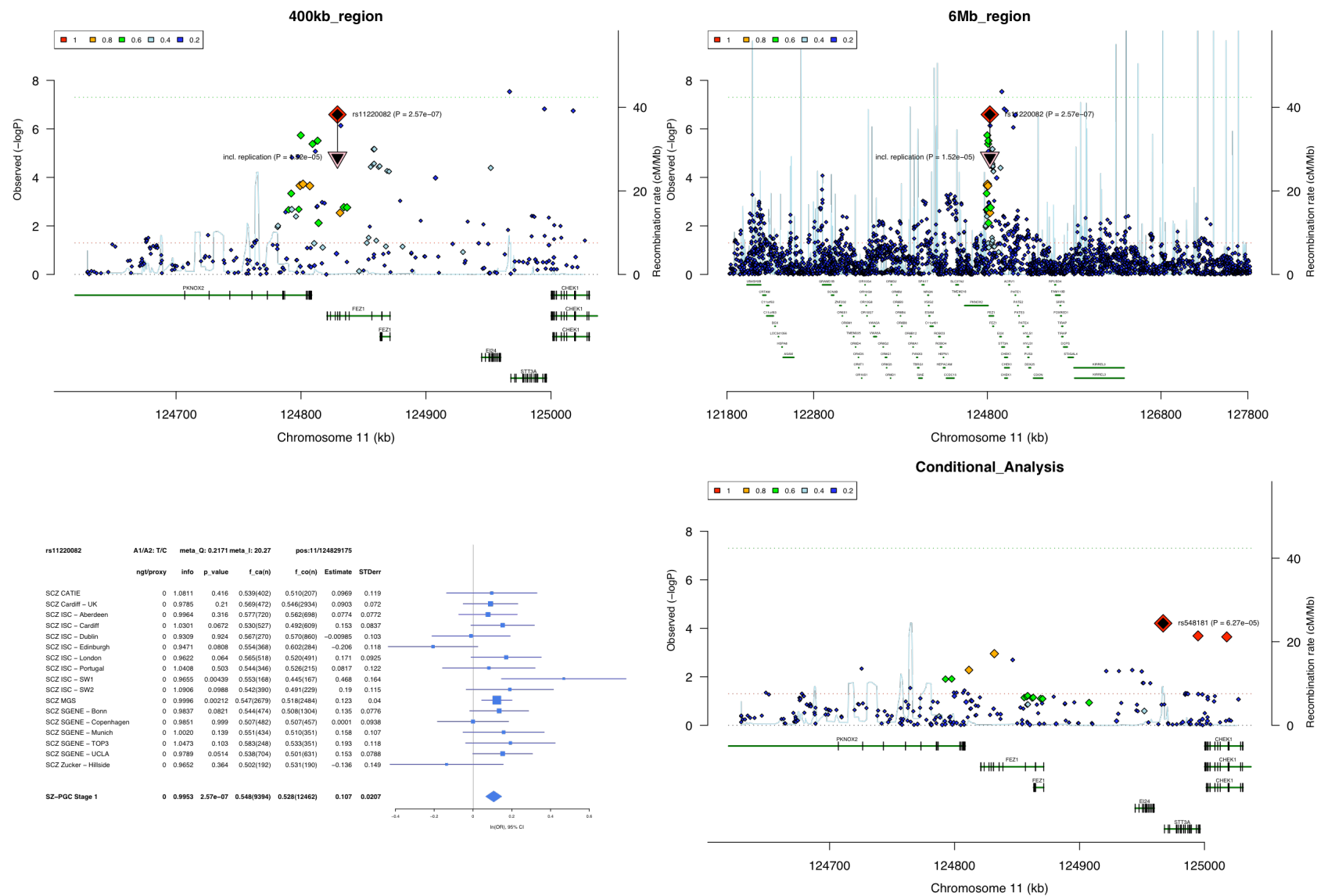


Figure S5: Region and Forest Plots – rs11191732.



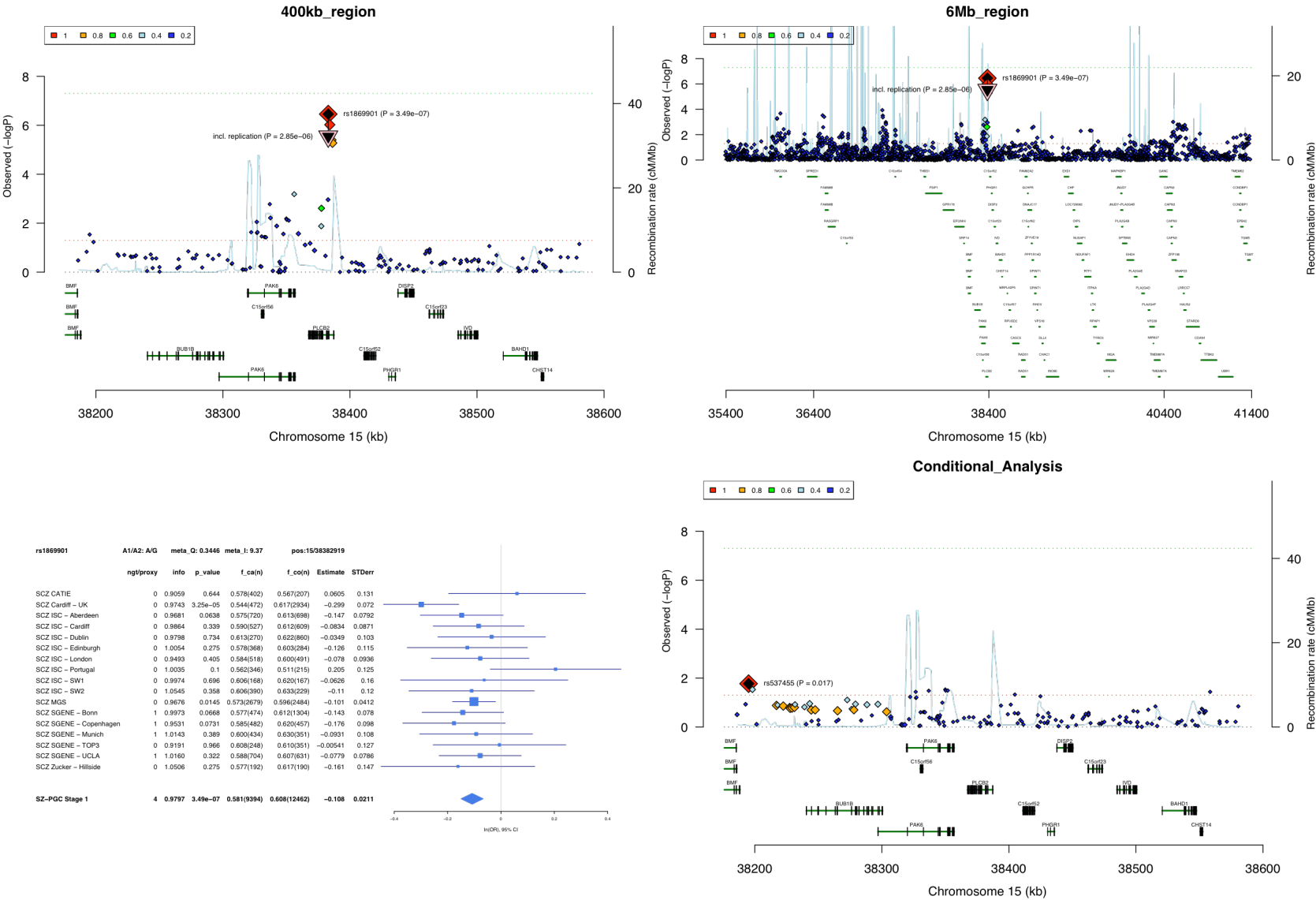
SZ\_PGC, Supplementary Materials - S43

Figure S5: Region and Forest Plots – rs11220082.



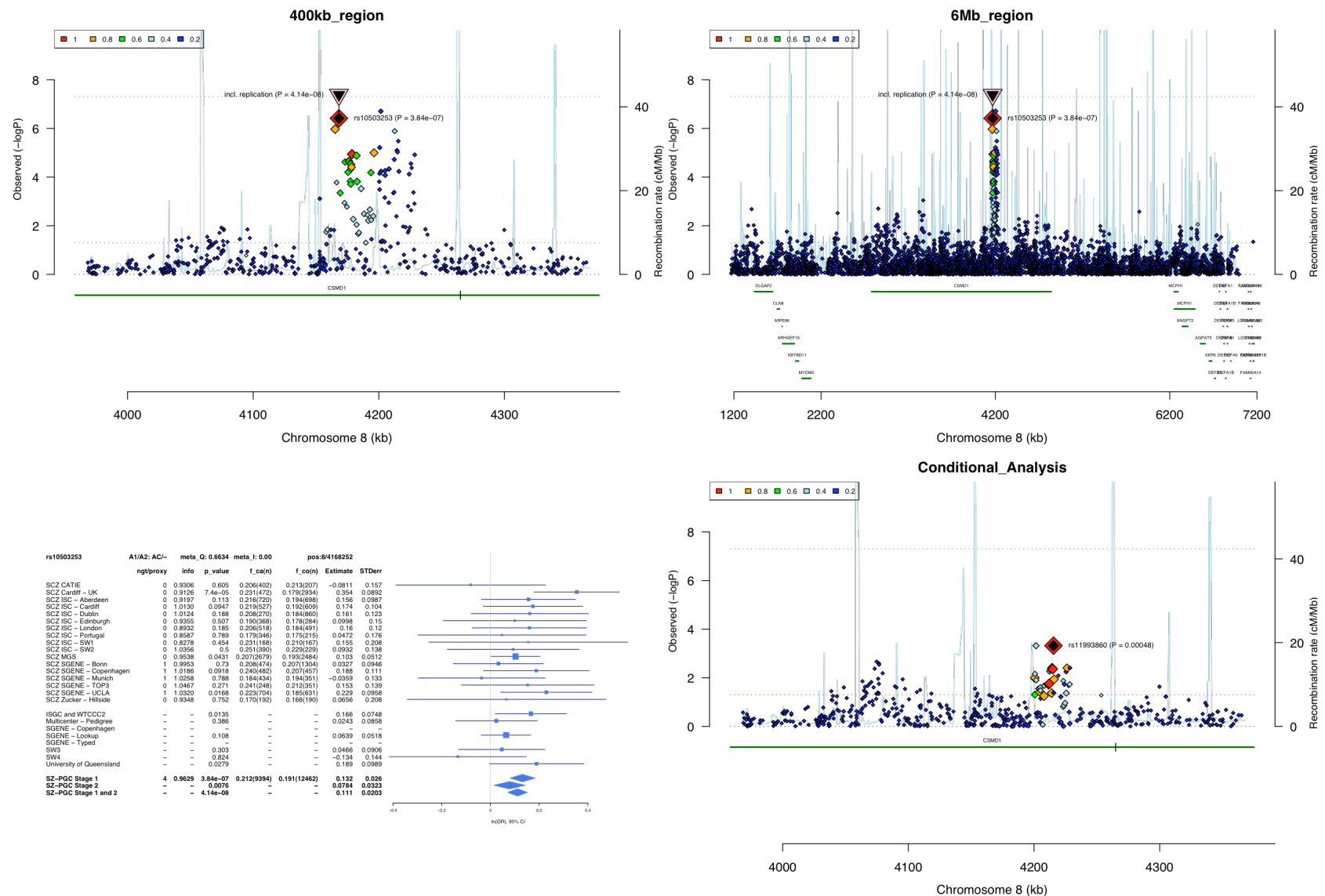
SZ\_PGC, Supplementary Materials - S44

Figure S5: Region and Forest Plots – rs1869901.



SZ\_PGC, Supplementary Materials - S45

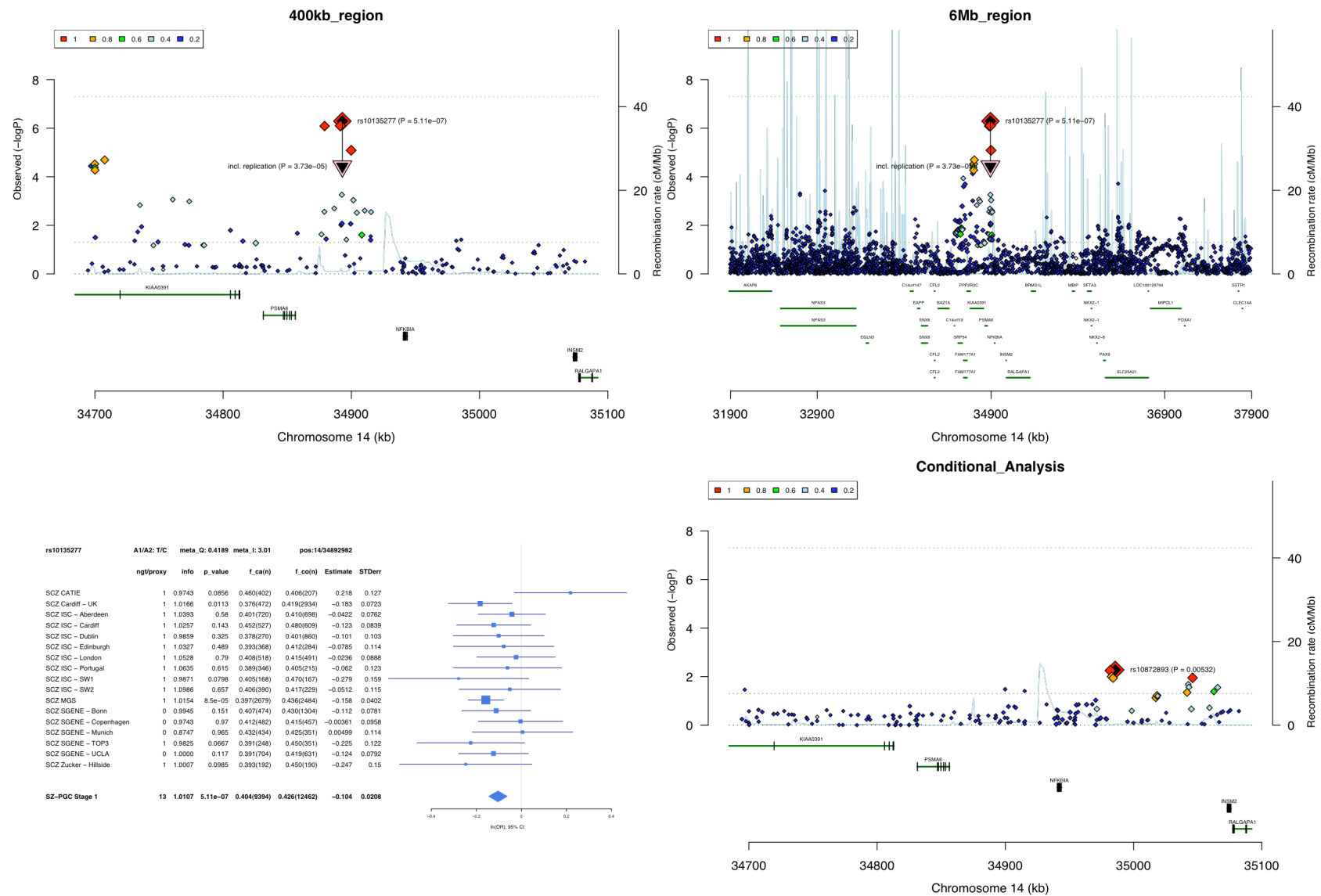
Figure S5: Region and Forest Plots – rs10503253.



SZ\_PGC, Supplementary Materials - S46

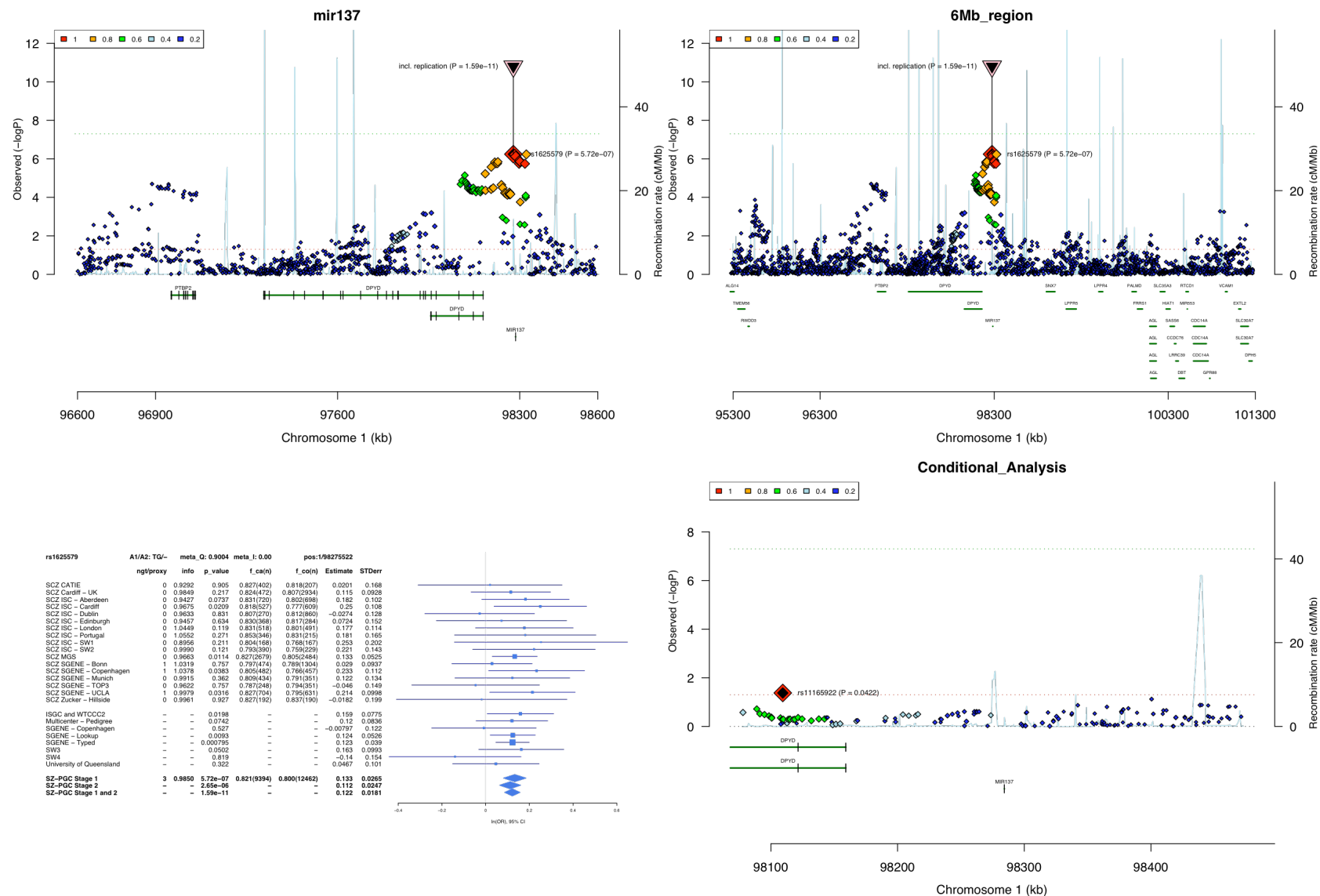


Figure S5: Region and Forest Plots – rs10135277.



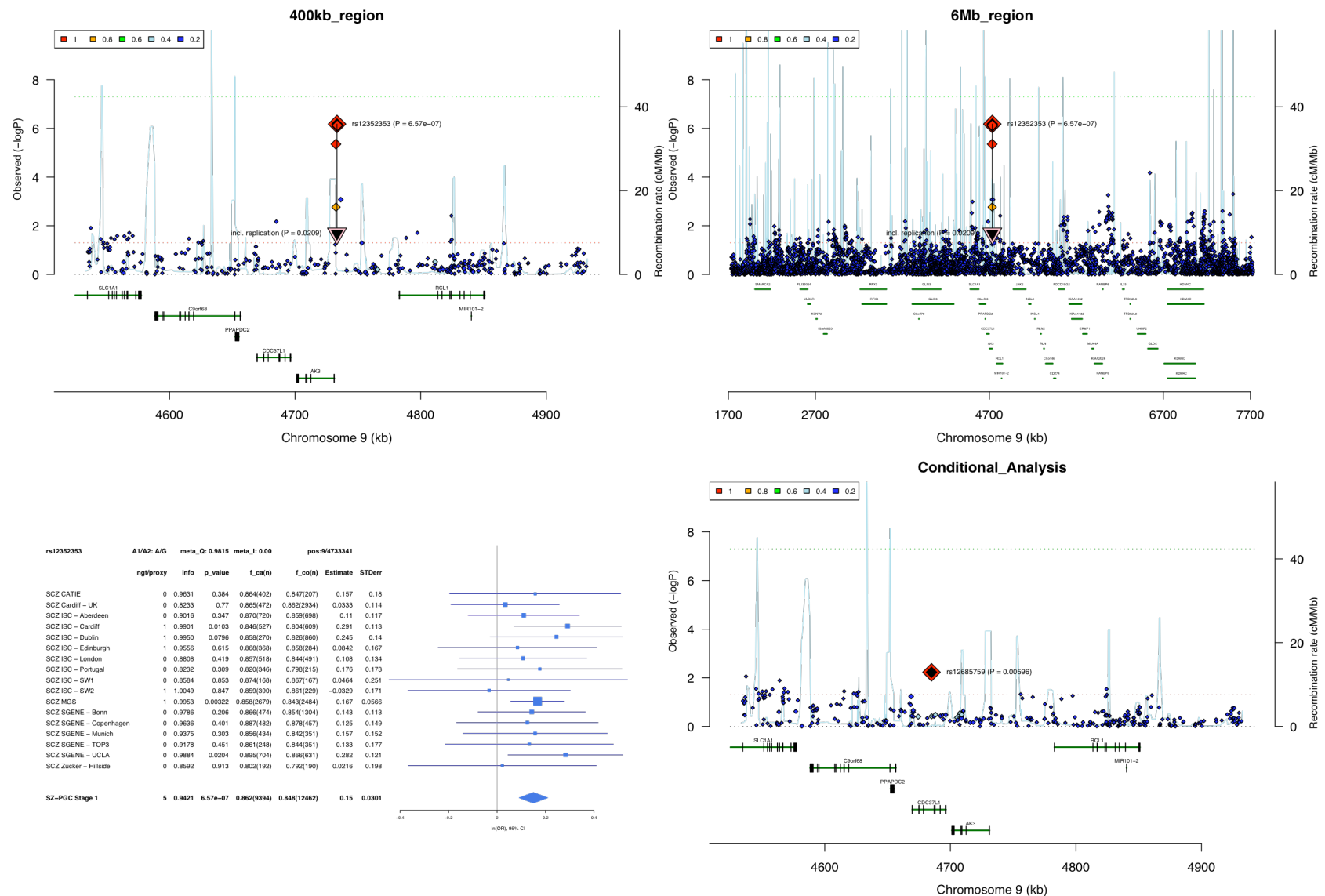
SZ\_PGC, Supplementary Materials - S47

Figure S5: Region and Forest Plots – rs1625579.



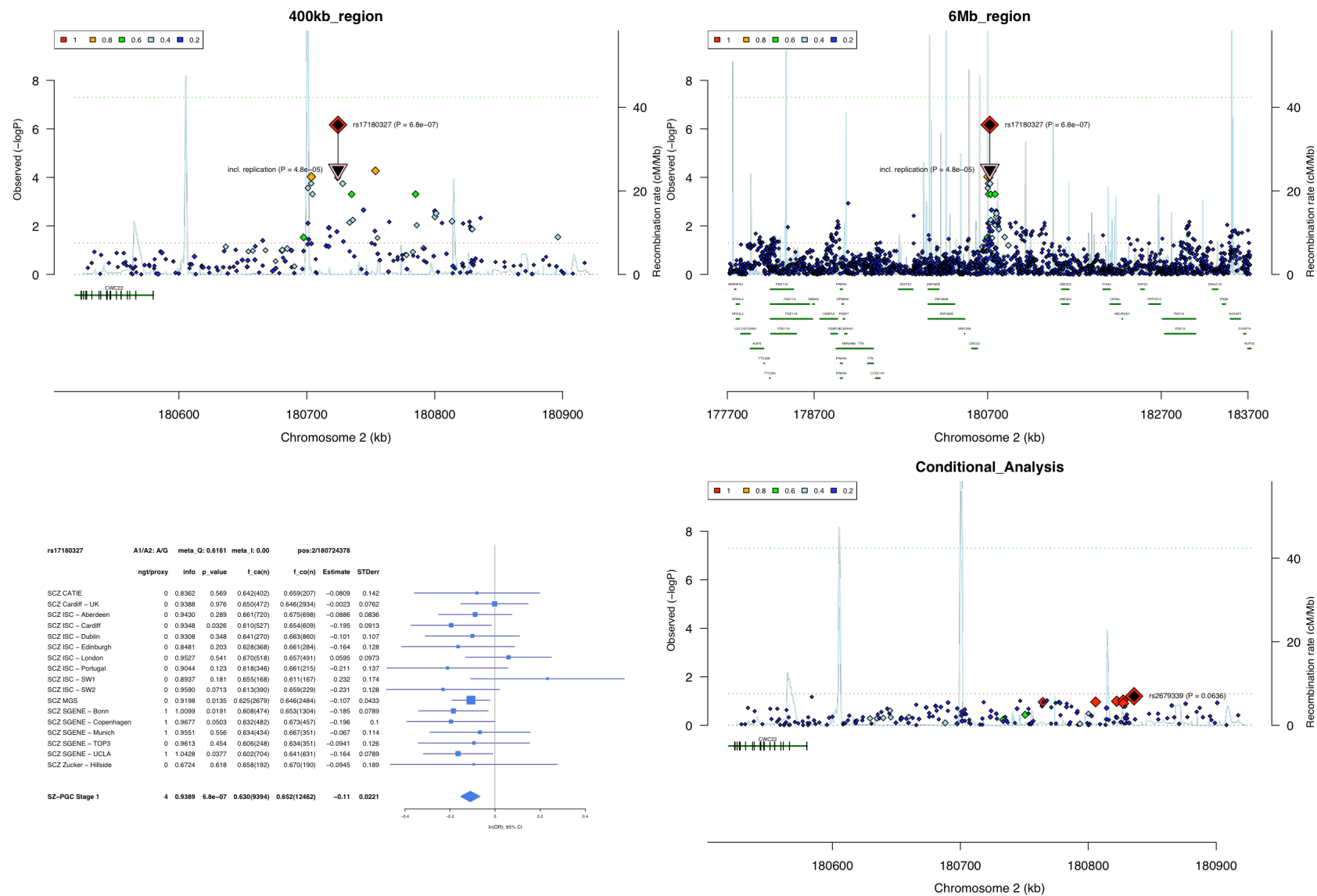
SZ\_PGC, Supplementary Materials - S48

Figure S5: Region and Forest Plots – rs12352353.



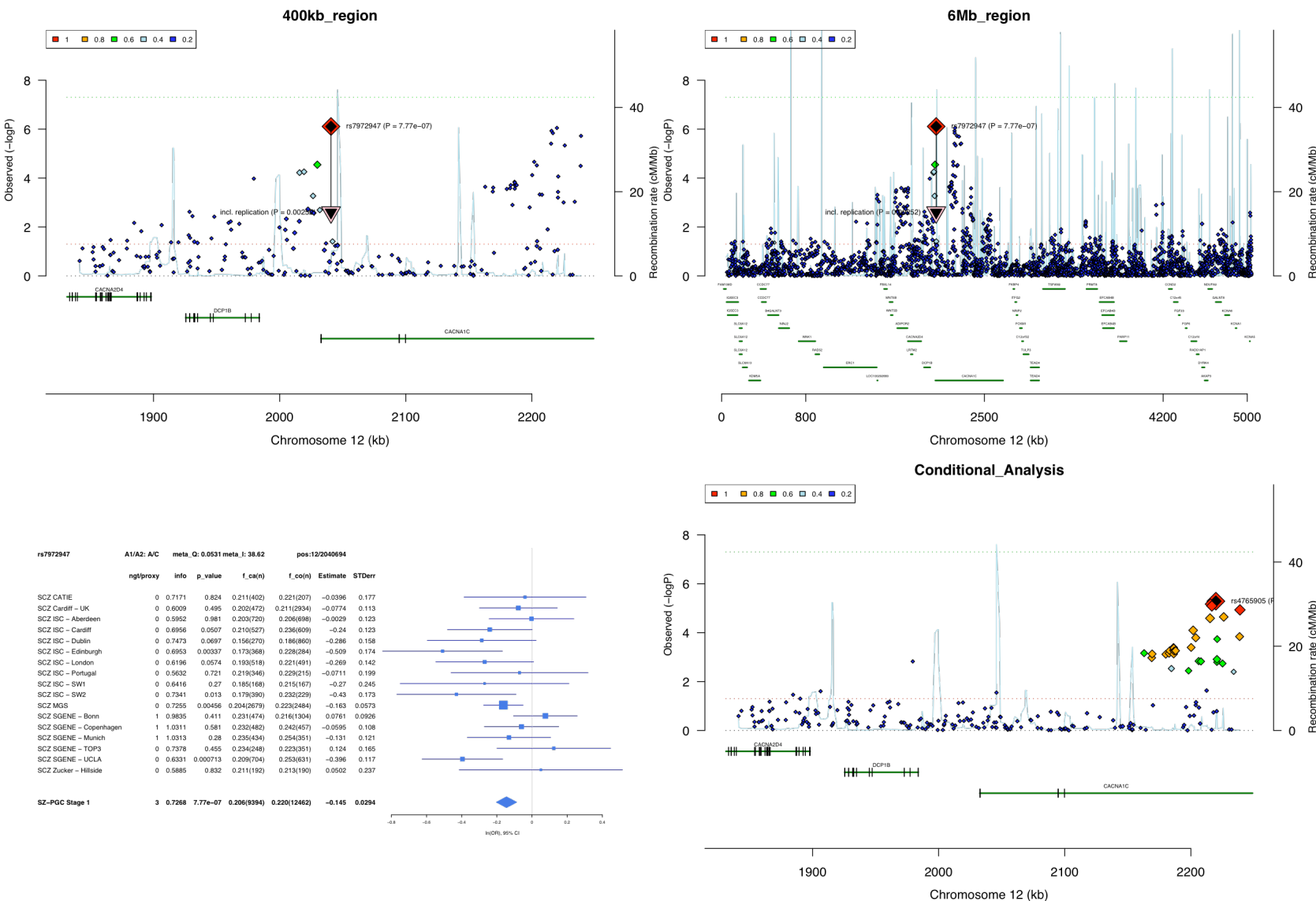
SZ\_PGC, Supplementary Materials - S49

Figure S5: Region and Forest Plots – rs17180327.



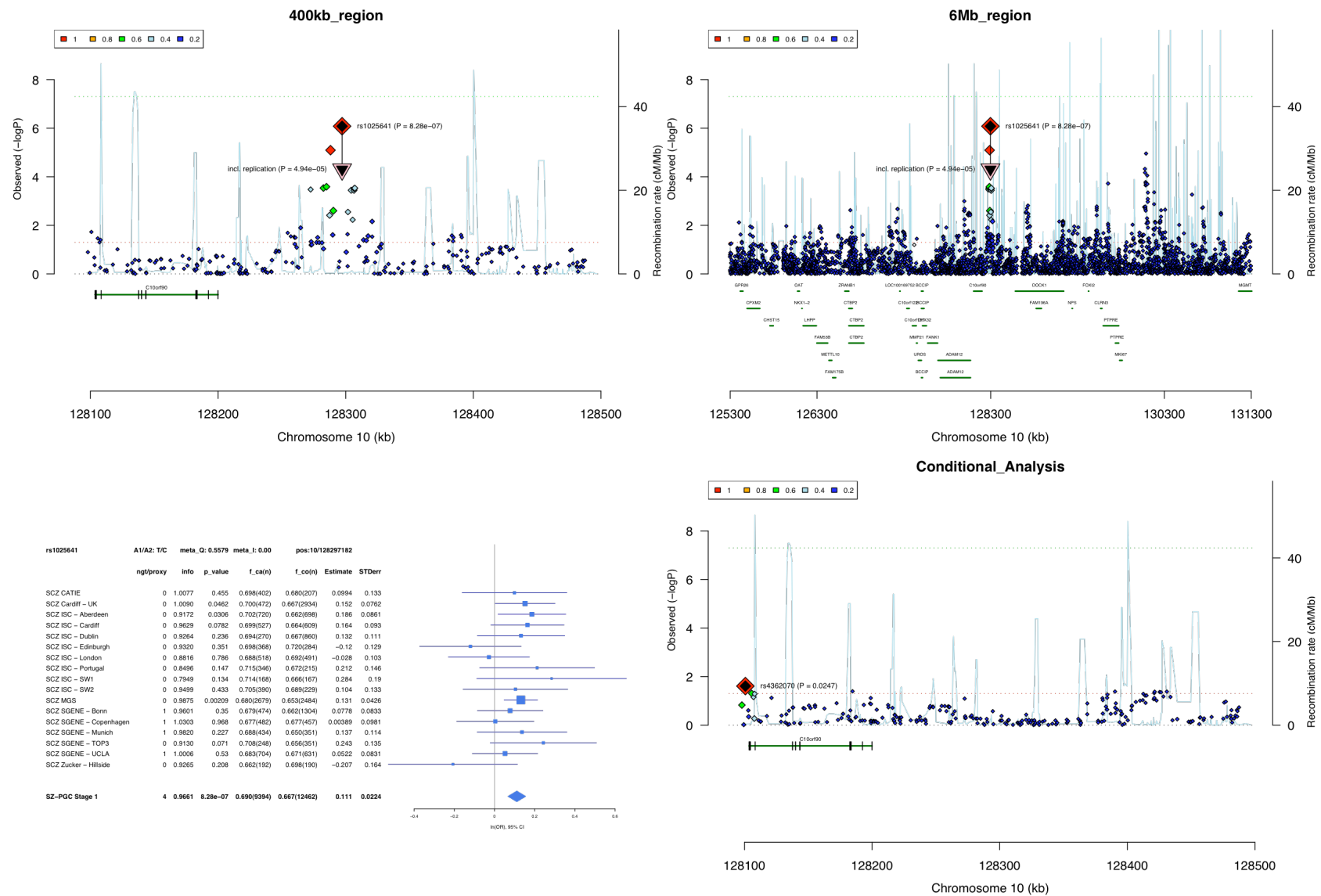
SZ\_PGC, Supplementary Materials - S50

Figure S5: Region and Forest Plots – rs7972947.



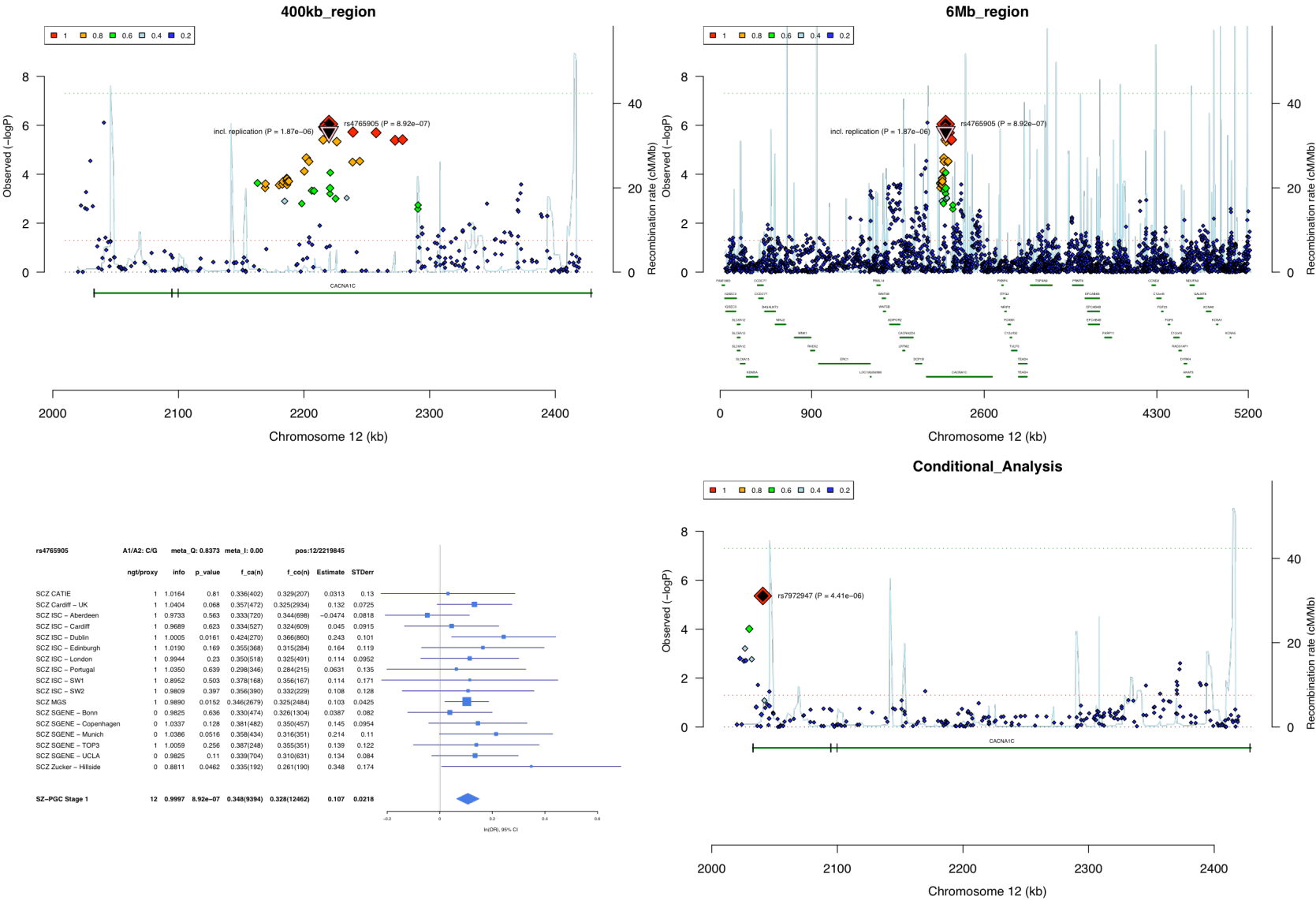
SZ\_PGC, Supplementary Materials - S51

Figure S5: Region and Forest Plots – rs1025641.



SZ\_PGC, Supplementary Materials - S52

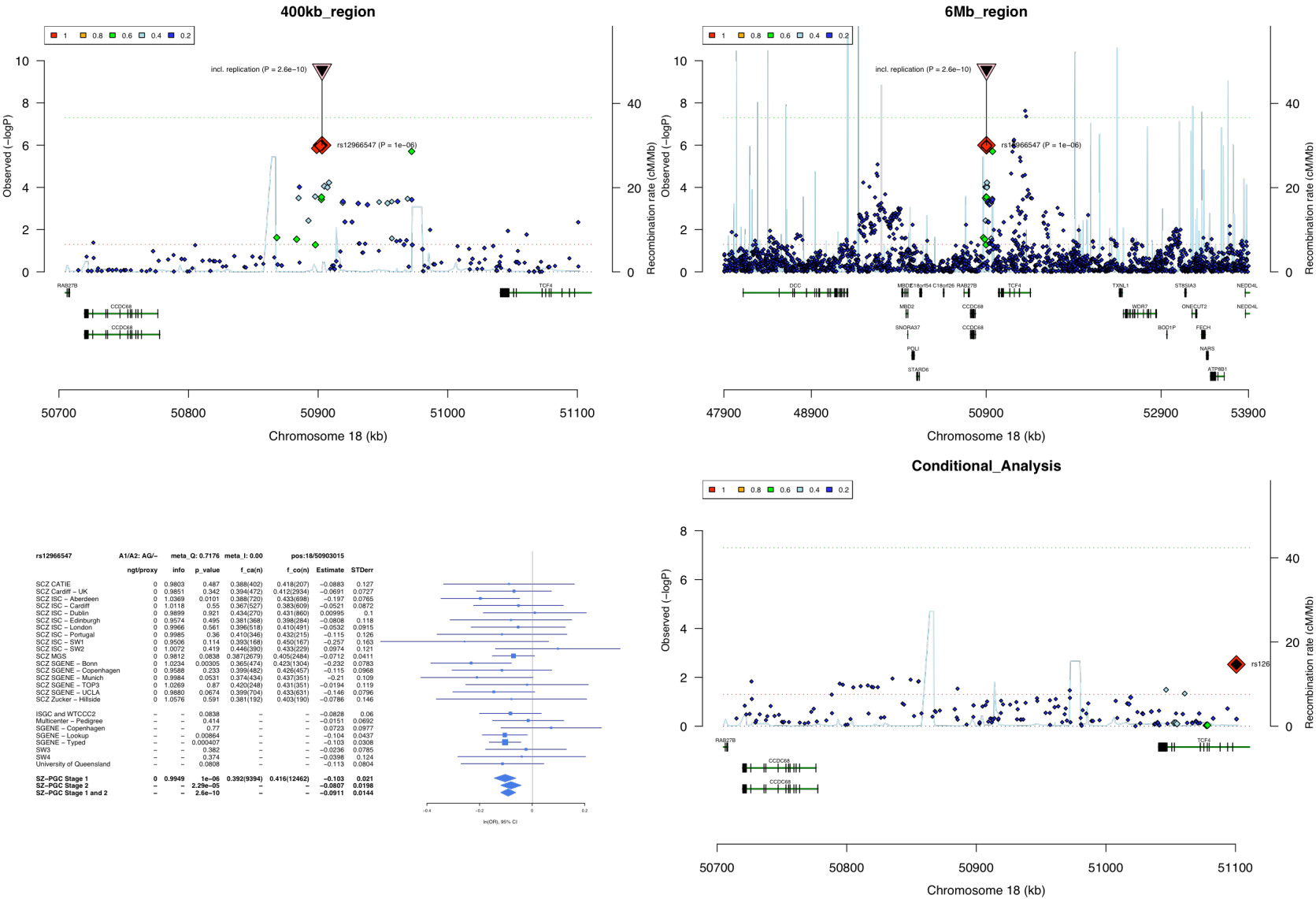
Figure S5: Region and Forest Plots – rs4765905.



SZ\_PGC, Supplementary Materials - S53

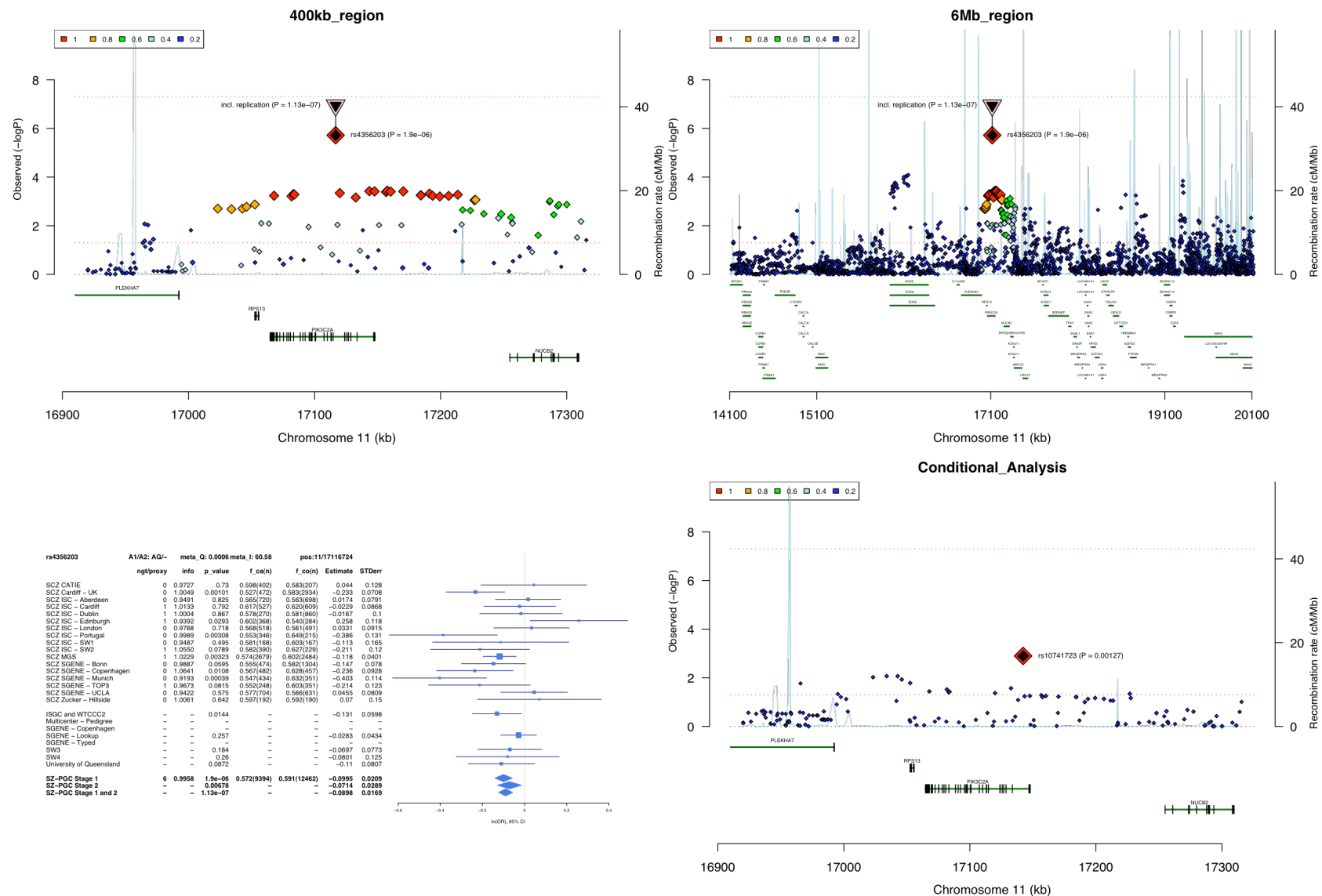


Figure S5: Region and Forest Plots – rs12966547.



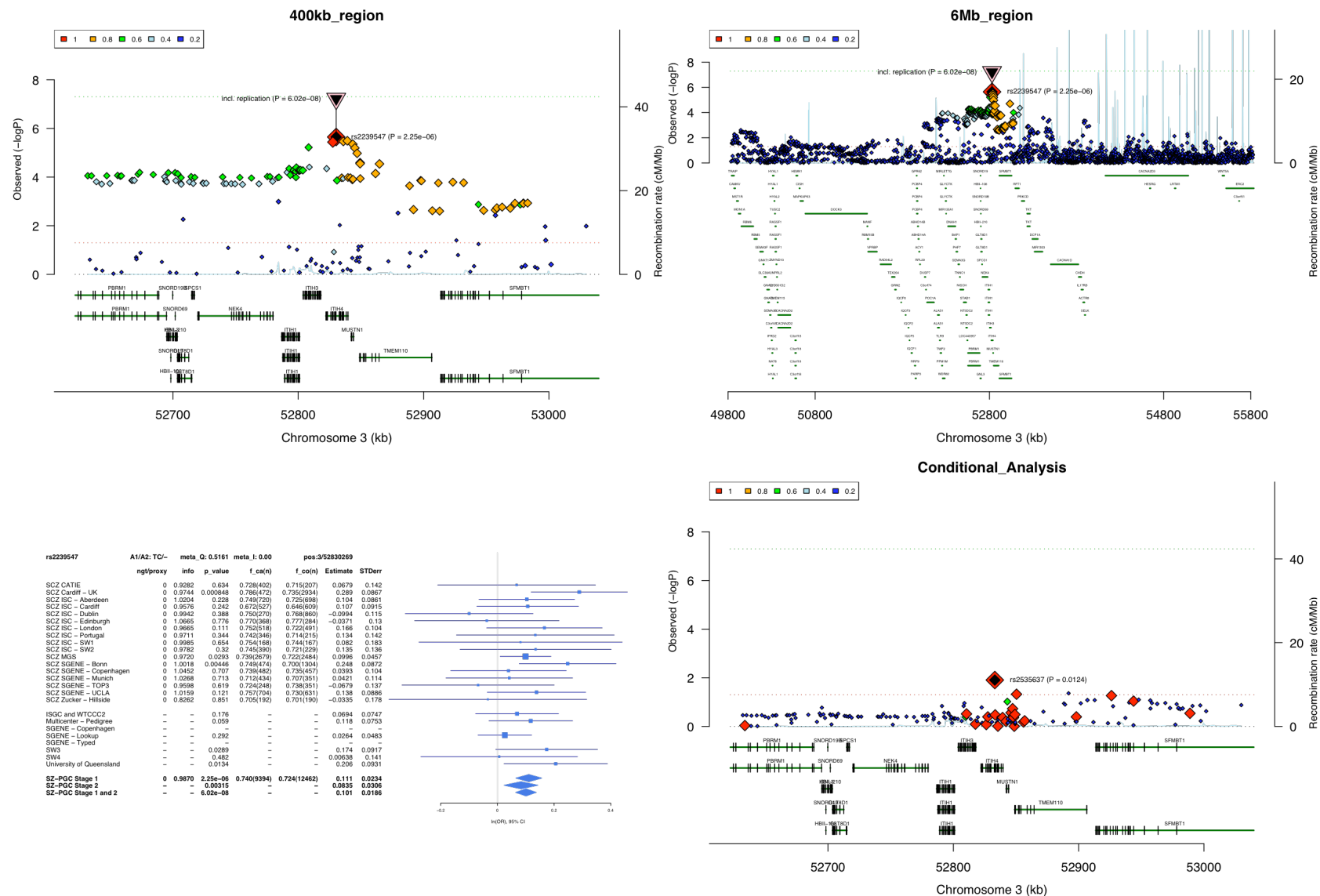
SZ\_PGC, Supplementary Materials - S54

Figure S5: Region and Forest Plots – rs4356203.



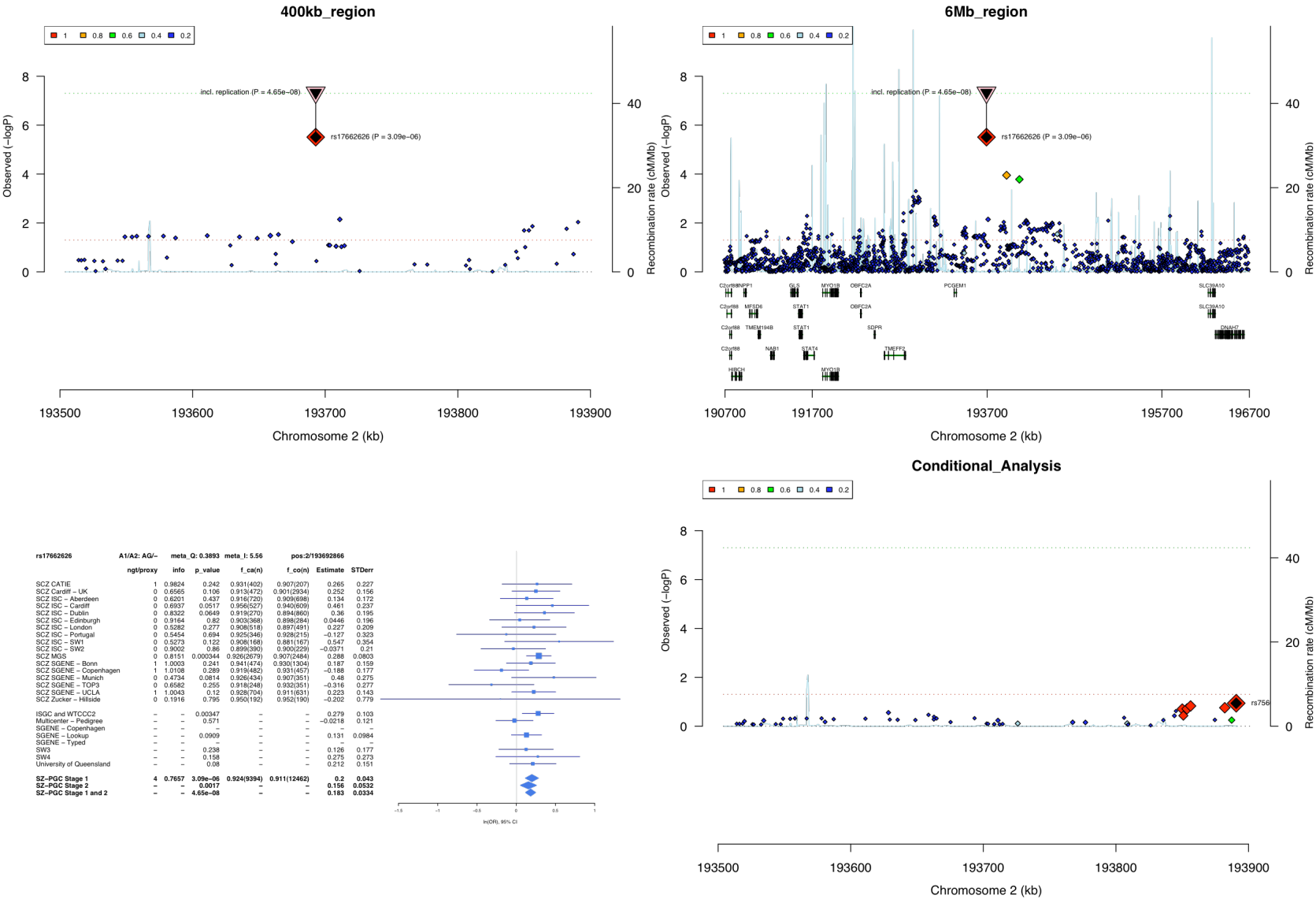
SZ\_PGC, Supplementary Materials - S55

Figure S5: Region and Forest Plots – rs2239547.



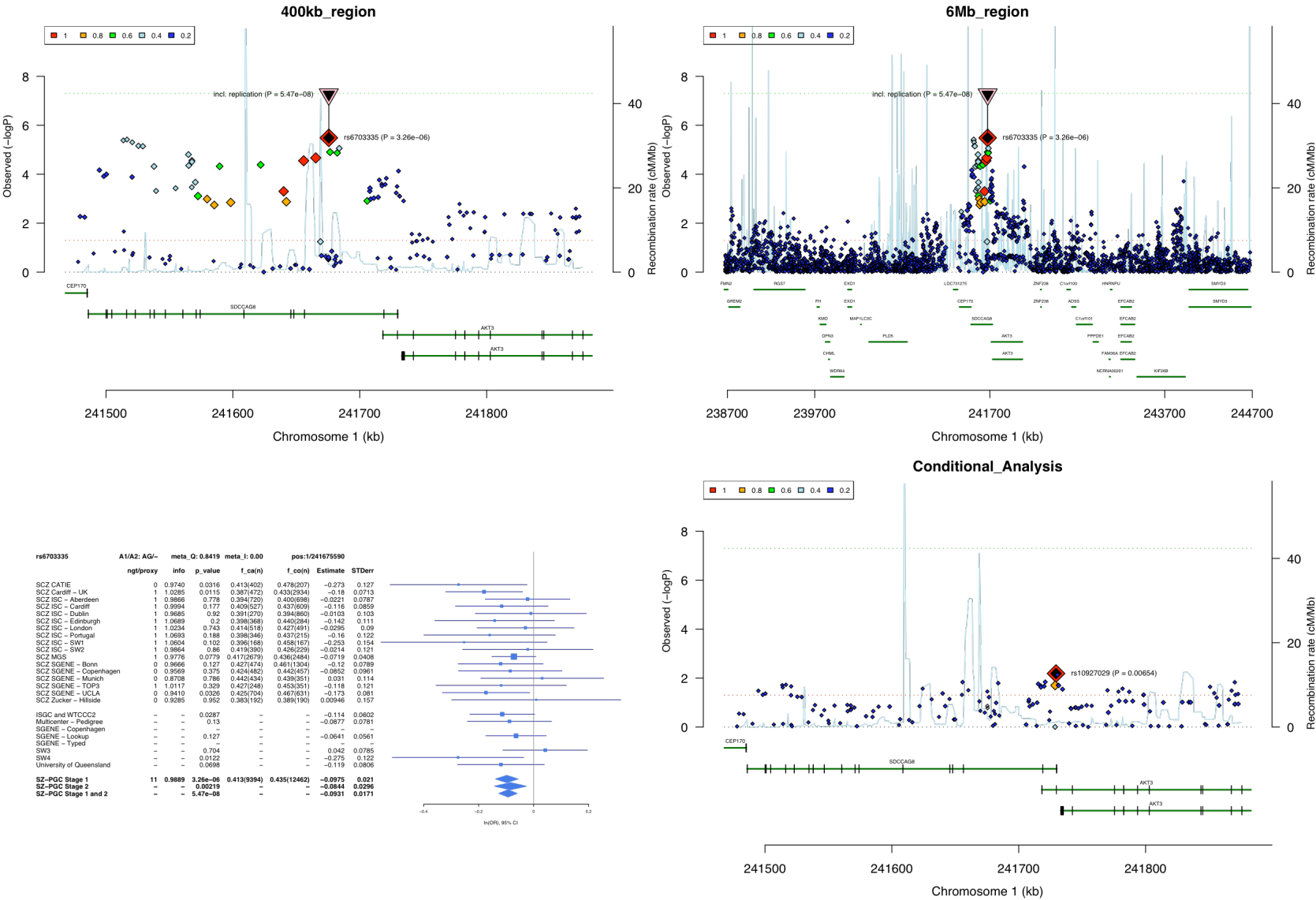
SZ\_PGC, Supplementary Materials - S56

Figure S5: Region and Forest Plots – rs17662626.



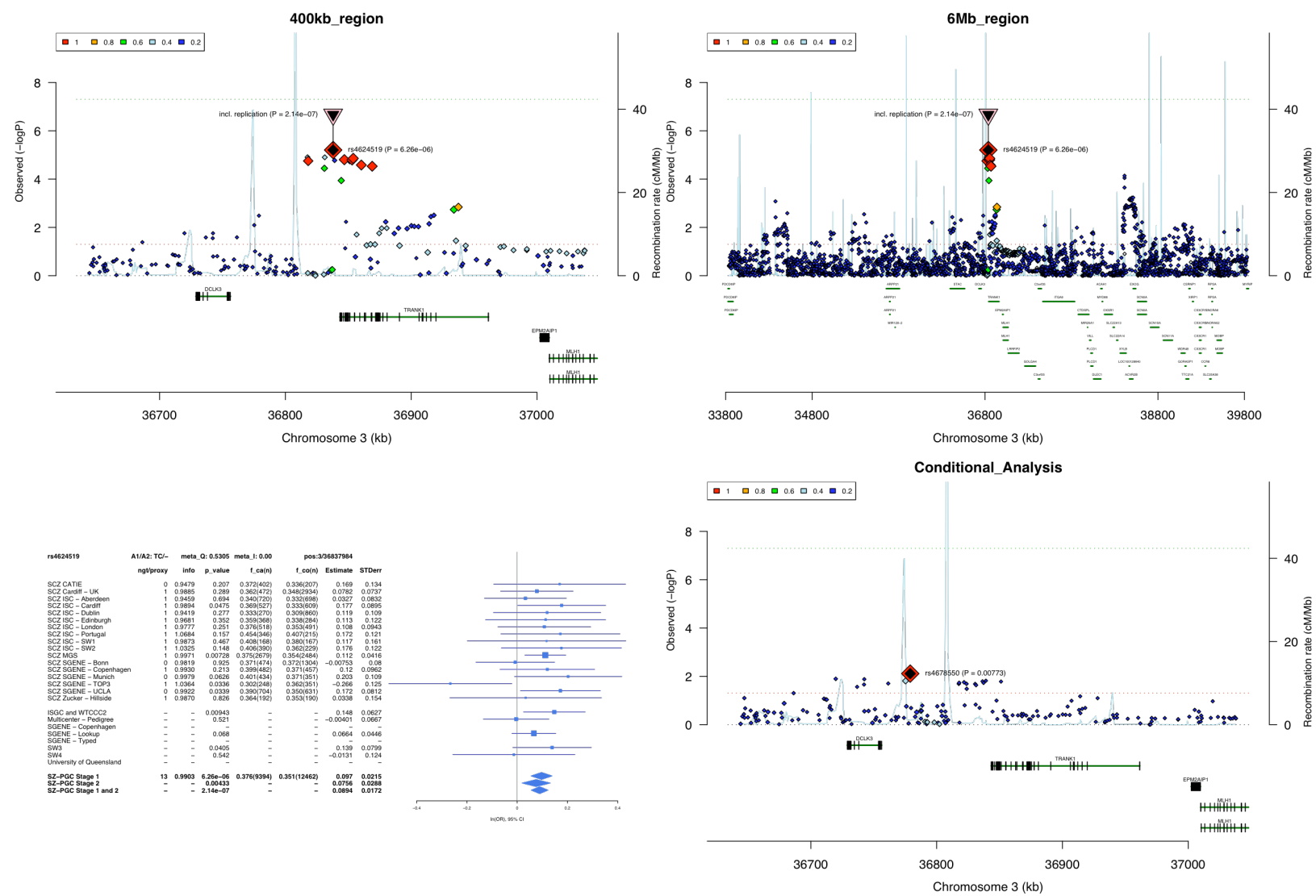
SZ\_PGC, Supplementary Materials - S57

Figure S5: Region and Forest Plots – rs6703335.



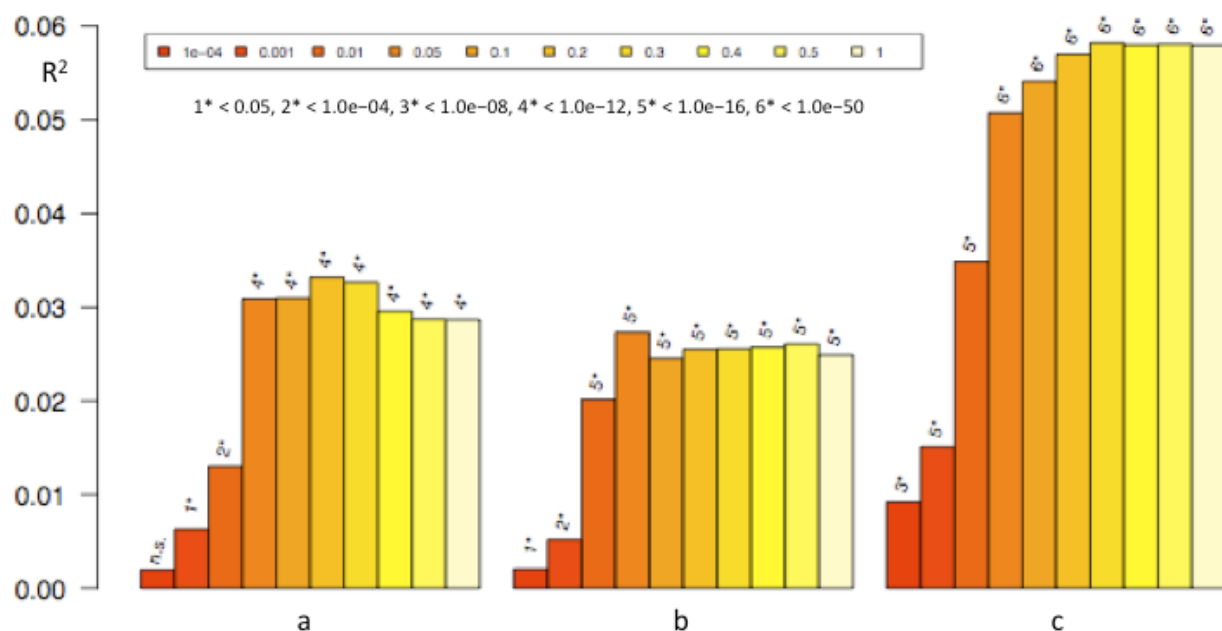
SZ\_PGC, Supplementary Materials - S58

Figure S5: Region and Forest Plots – rs4624519.



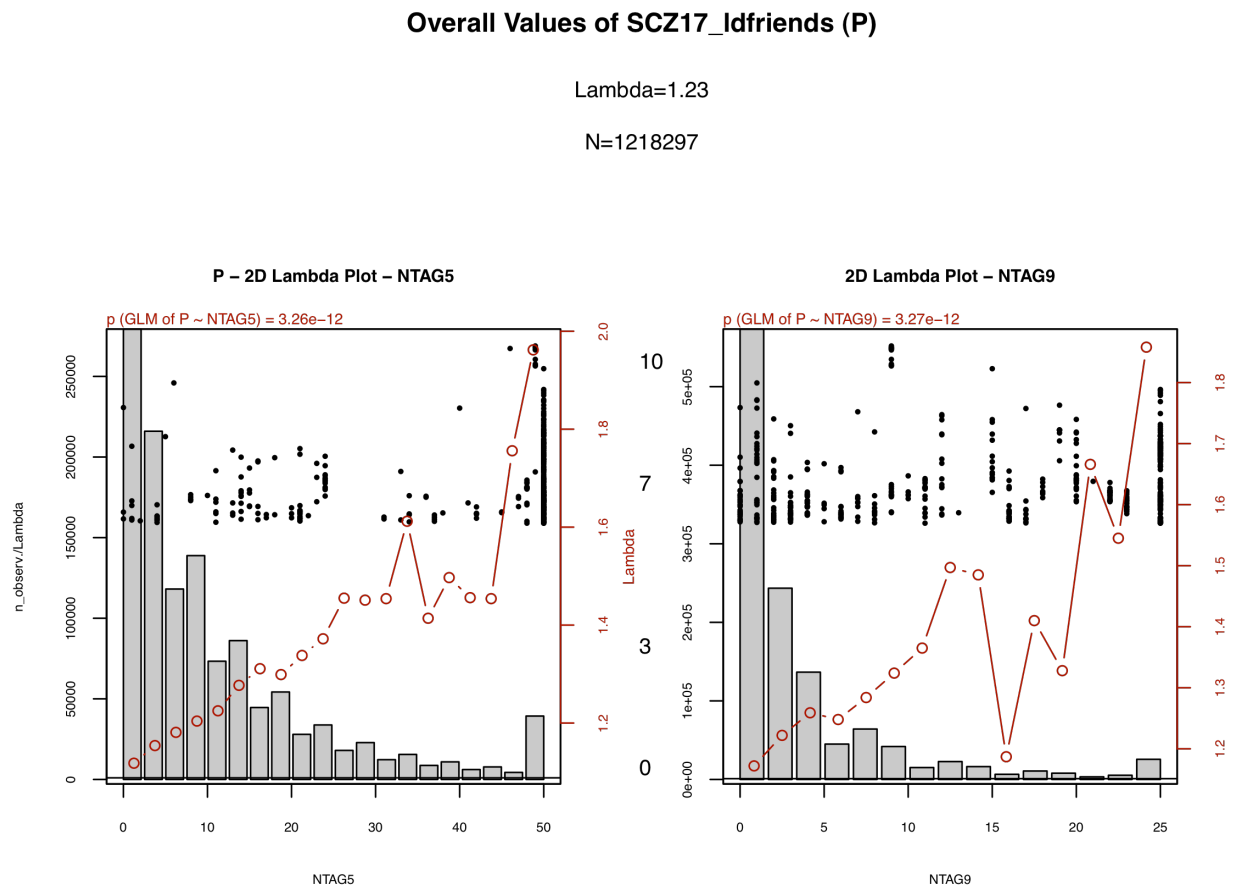
SZ\_PGC, Supplementary Materials - S59

**Figure S6: Polygenic Analysis.** Polygene analysis of the SZ-PGC Stage 1 scan compared with the previously published ISC results. The current training set consists of the ISC<sup>13</sup>, MGS<sup>10</sup>, and Cardiff<sup>4</sup> scans' results with the remaining samples utilized as the test. Plotted for comparison are the previously published results of ISC (training) with Cardiff (test) and MGS (test). The three x-axis groupings are (a) ISC → Cardiff, (b) ISC → MGS, and (c) ISC + Cardiff + MGS → Stage 1 remnant. Color-coding denotes the gradient of  $p$ -value thresholds,  $pT$ 's (deep orange  $p < 0.0001$ ,  $p < 0.001$ ,  $p < 0.01$ ,  $p < 0.05$ ,  $p < 0.1$ ,  $p < 0.2$ ,  $p < 0.3$ ,  $p < 0.4$ ,  $p < 0.5$ , and  $p < 1.0$  light yellow). As predicted in the ISC publication, the variance explained (estimated via Nagelkerke's pseudo  $r^2$  plotted on the y-axis) is substantially increased and achieves a near maximum value at a lower  $p$ -value. Both of these features signify the greater power (i.e., greater excess of truly associated variants at low  $p$ -values) of the current study. The number of stars demonstrate the significance of the analysis, with 1\* through 6\*, corresponding to values of  $p < 0.05$ ,  $10^{-04}$ ,  $10^{-08}$ ,  $10^{-12}$ ,  $10^{-16}$ ,  $10^{-50}$ . These values should not be confused with the  $p$ -value thresholds ( $pT$ 's) used for selection of training SNPs, reflected by the orange shading.

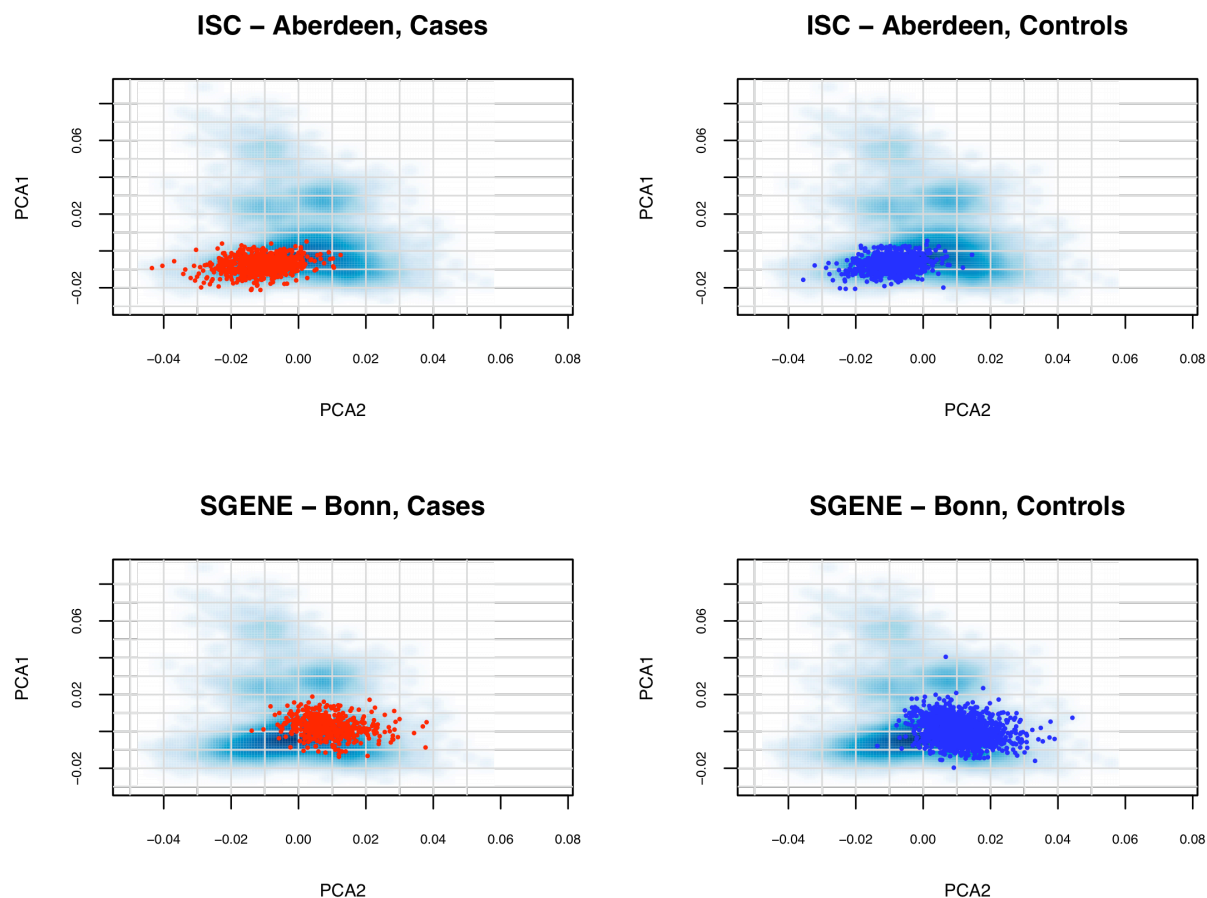




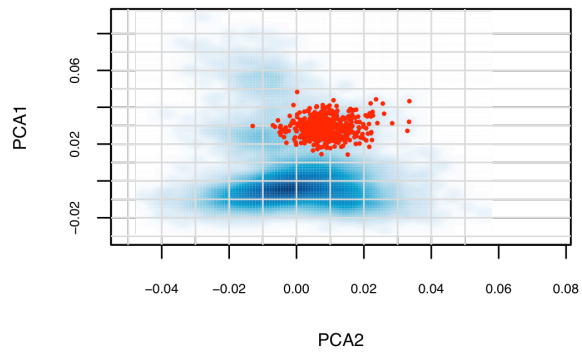
**Figure S7: Overall Values of Stage 1 LD-friends.** Shown here are patterns of  $\lambda$ -behavior as a function of SNPs with higher or lower number of neighboring SNPs in LD. The x-axis enumerates SNPs with the number of LD friends indicated, with either  $r^2 > 0.5$  (left plot) or  $r^2 > 0.9$  (right plot). The red line and red (right) y-scale indicate the  $\lambda_{GC}$ . The gray bars with black (left) y-scale indicate the size of bin. The black dots with black (middle, between the two plots) y-scale indicate the  $p$ -values of all SNPs with a  $p < 1 \times 10^{-6}$  (presented in log-scale). SNPs with  $> 50$  LD-friends (left plot) and  $> 25$  LD-friends (right plot) are condensed into the far right bins (i.e., with 50 or 25 LD-friends, respectively). These plots show  $\lambda$  increasing with the number of LD-friends.



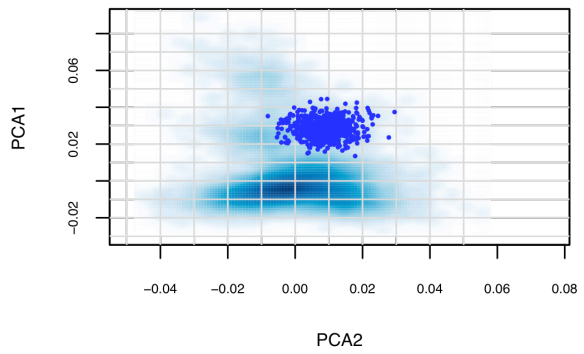
**Figure S8: Principal-Components Analysis (PCA) Plots.** To assess and correct for inflation due to population structure, we performed a principal-components (PC) analysis. Cases and controls are shown superimposed over a light version of the plot of all Stage 1 samples. The principal components were defined across all 17 Stage 1 samples using a set of markers that were genotyped in each study. PC1 and PC2 are shown. Multi-dimensional scaling (MDS) for all Stage 1 samples compared to HapMap3 anchors are displayed in Figure S12.



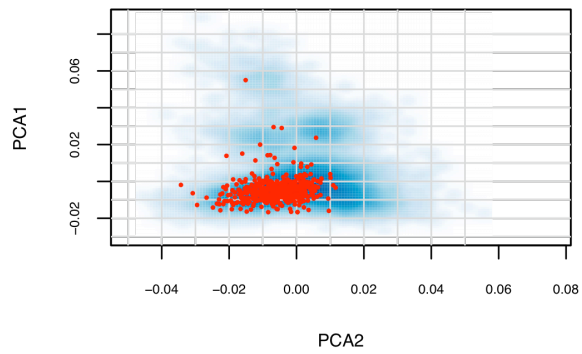
**ISC – Cardiff, Cases**



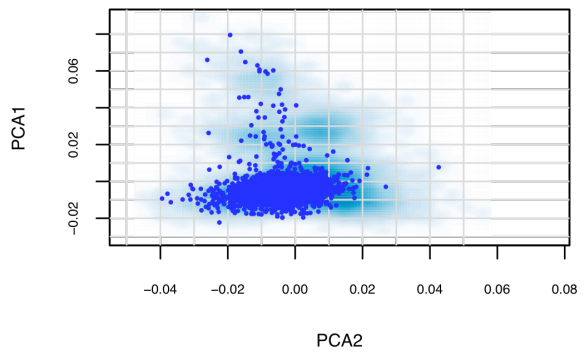
**ISC – Cardiff, Controls**



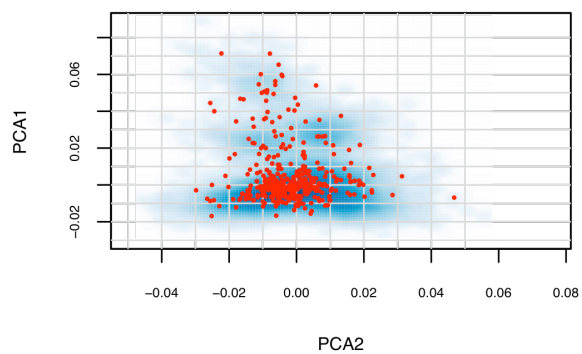
**Cardiff UK, Cases**



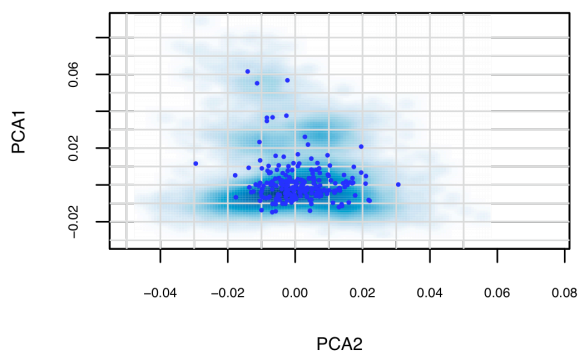
**Cardiff UK, Controls**



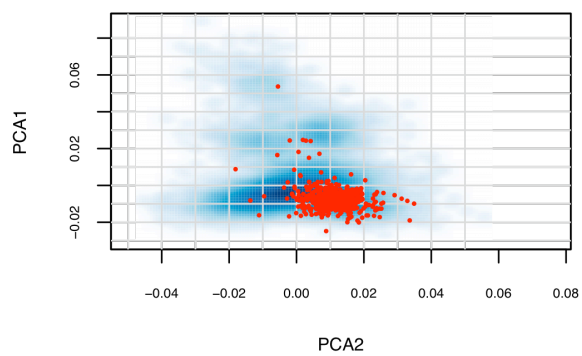
**CATIE, Cases**



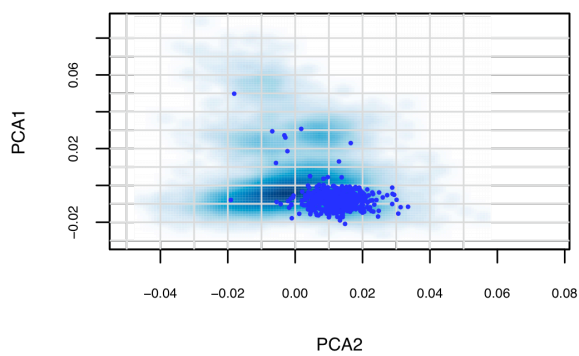
**CATIE, Controls**



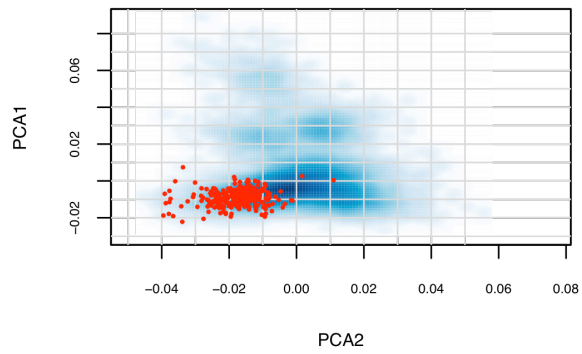
**SGENE – Copenhagen, Cases**



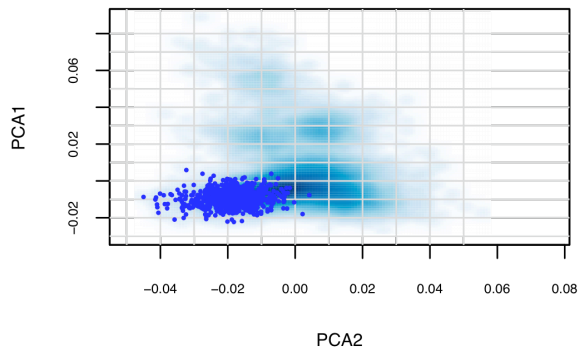
**SGENE – Copenhagen, Controls**



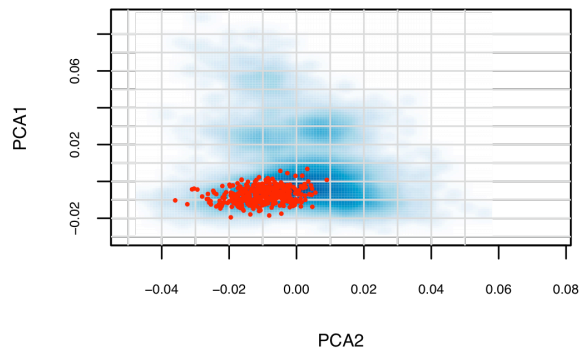
**ISC – Dublin, Cases**



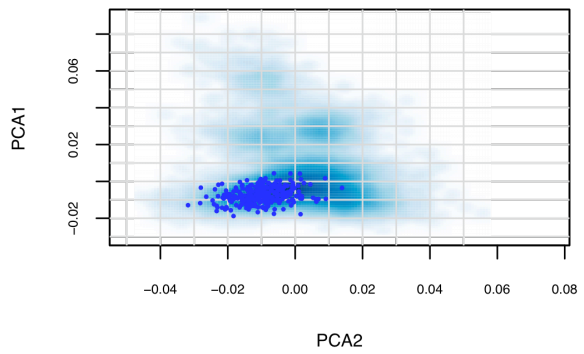
**ISC – Dublin, Controls**

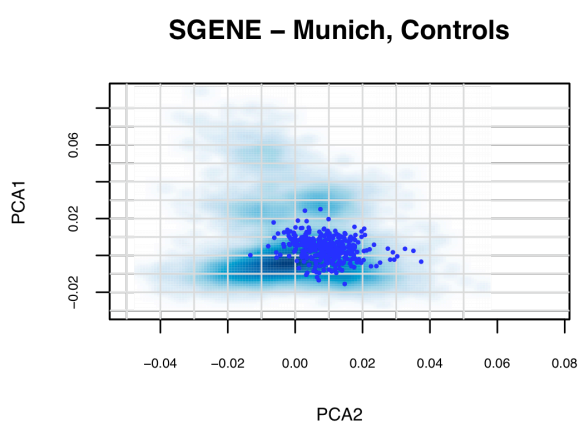
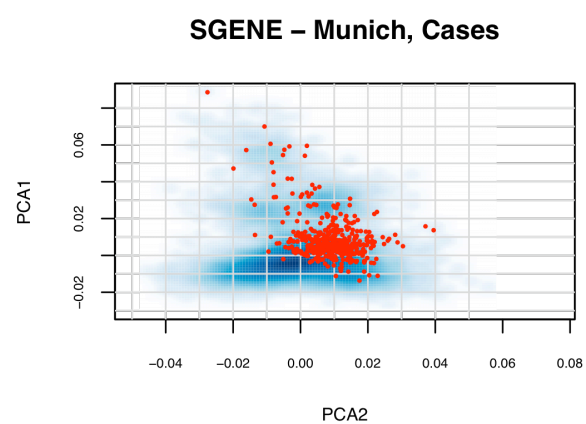
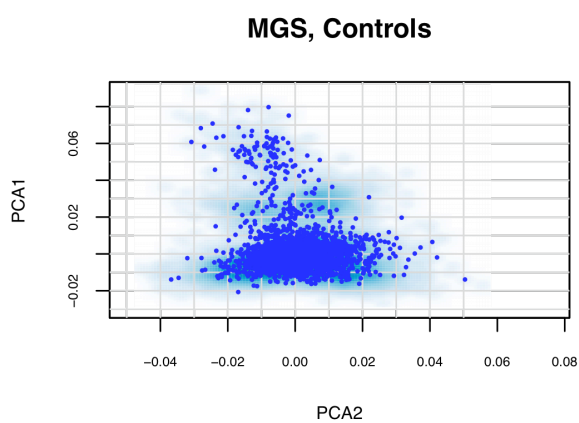
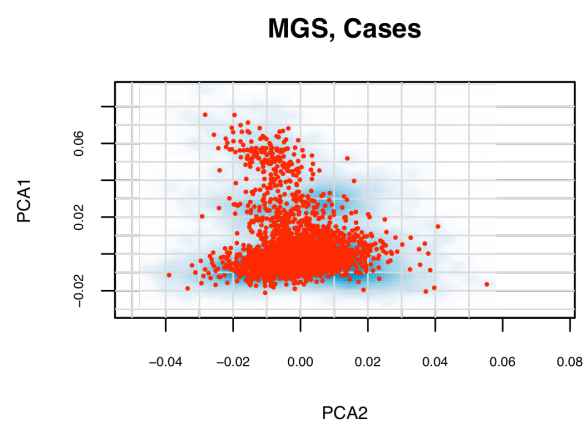


**ISC – Edinburgh, Cases**

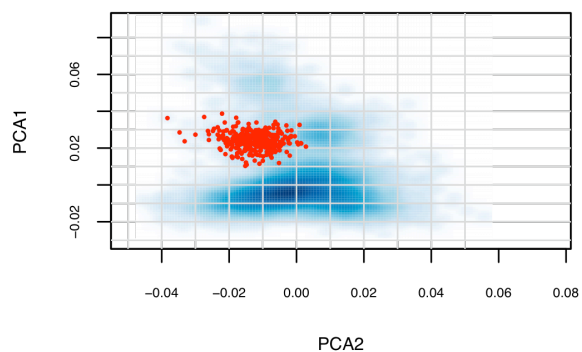


**ISC – Edinburgh, Controls**

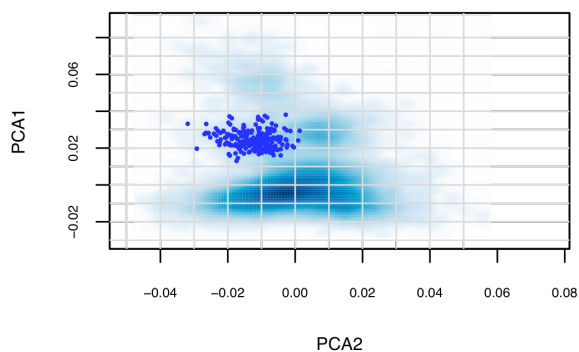




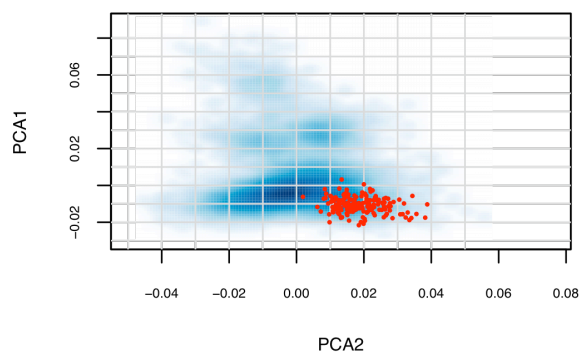
**ISC – Portugal, Cases**



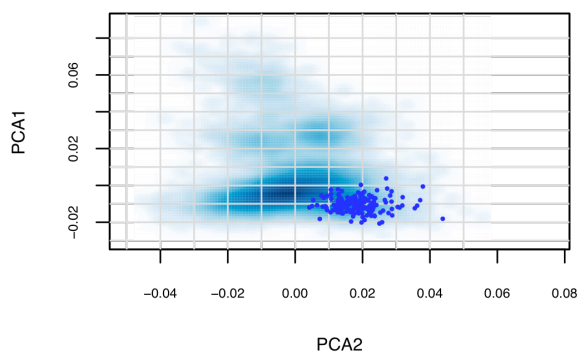
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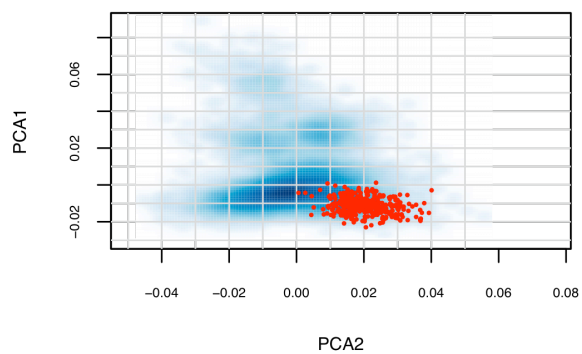
**ISC – SW1, Cases**



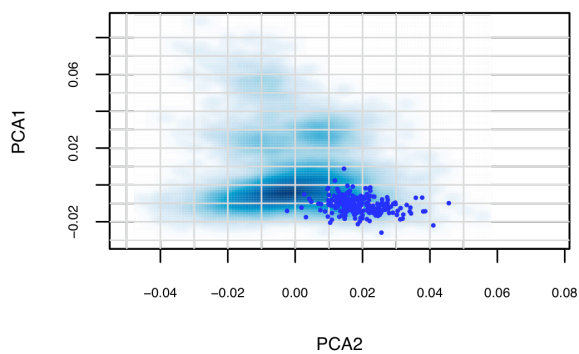
**ISC – SW1, Controls**



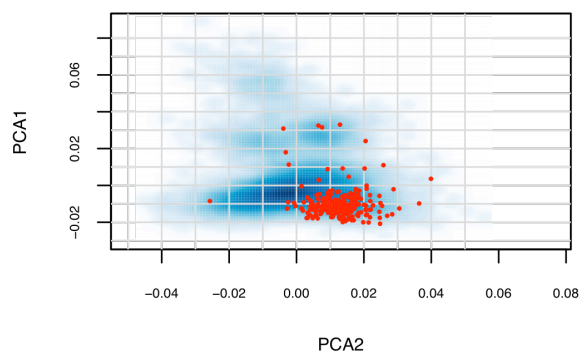
**ISC – SW2, Cases**



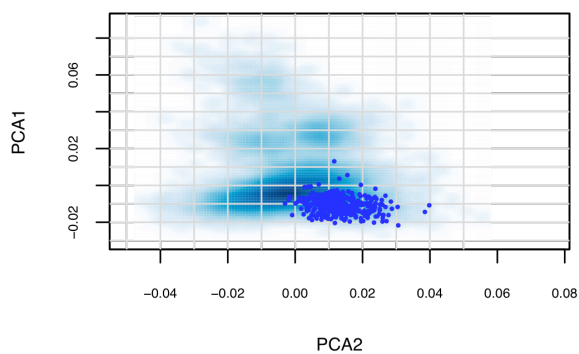
**ISC – SW2, Controls**



**SGENE – TOP3, Cases**

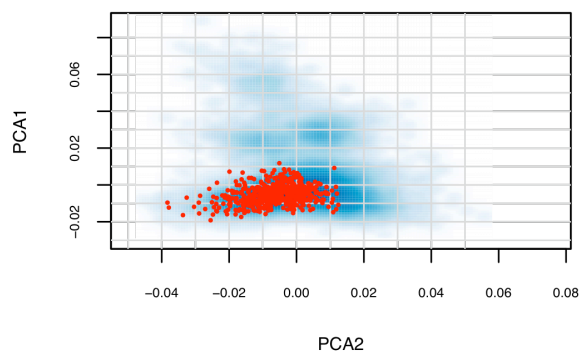


**SGENE – TOP3, Controls**

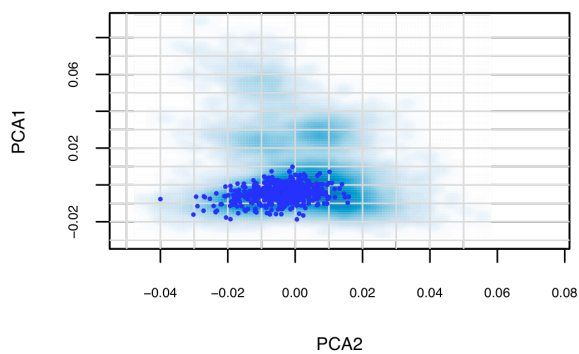




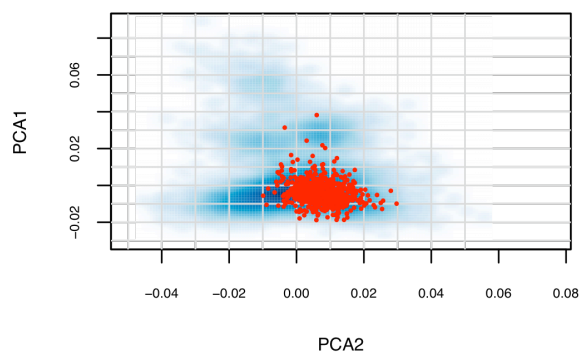
**ISC – London, Cases**



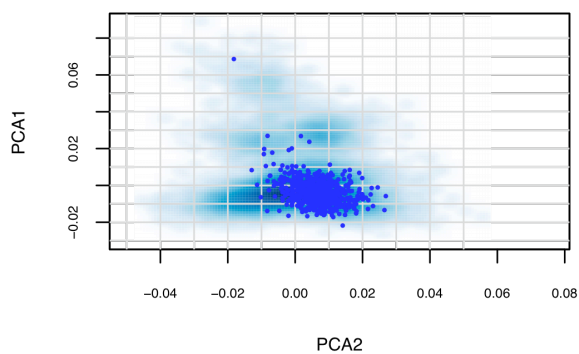
**ISC – London, Controls**

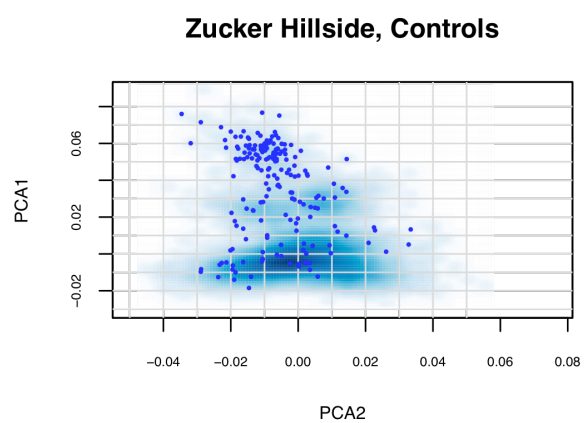
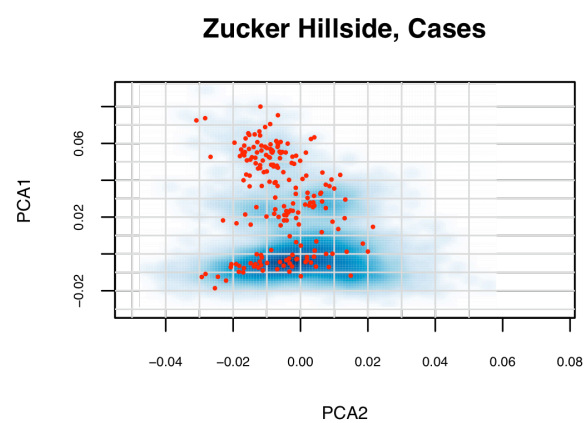


**SGENE – UCLA, Cases**

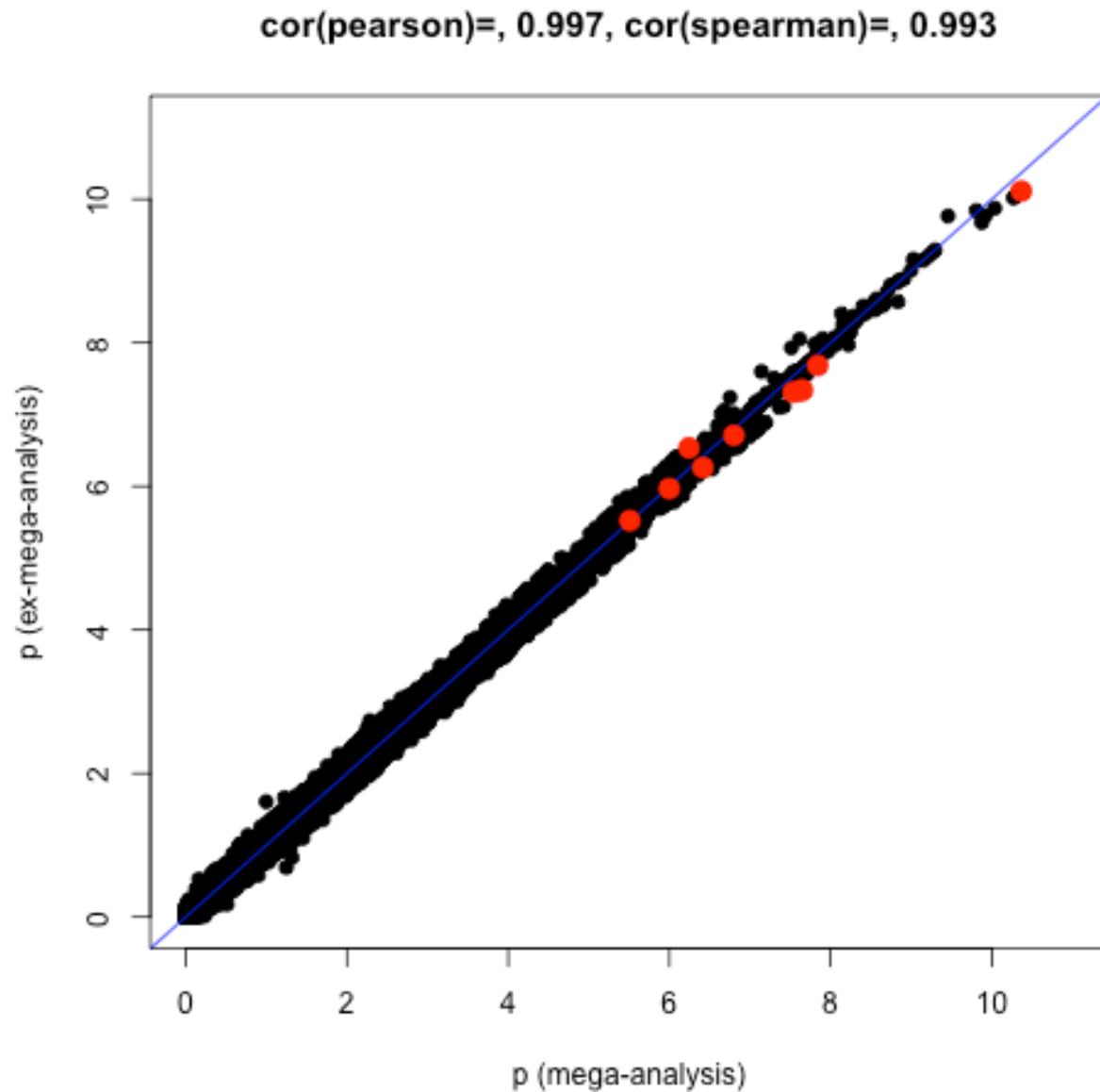


**SGENE – UCLA, Controls**

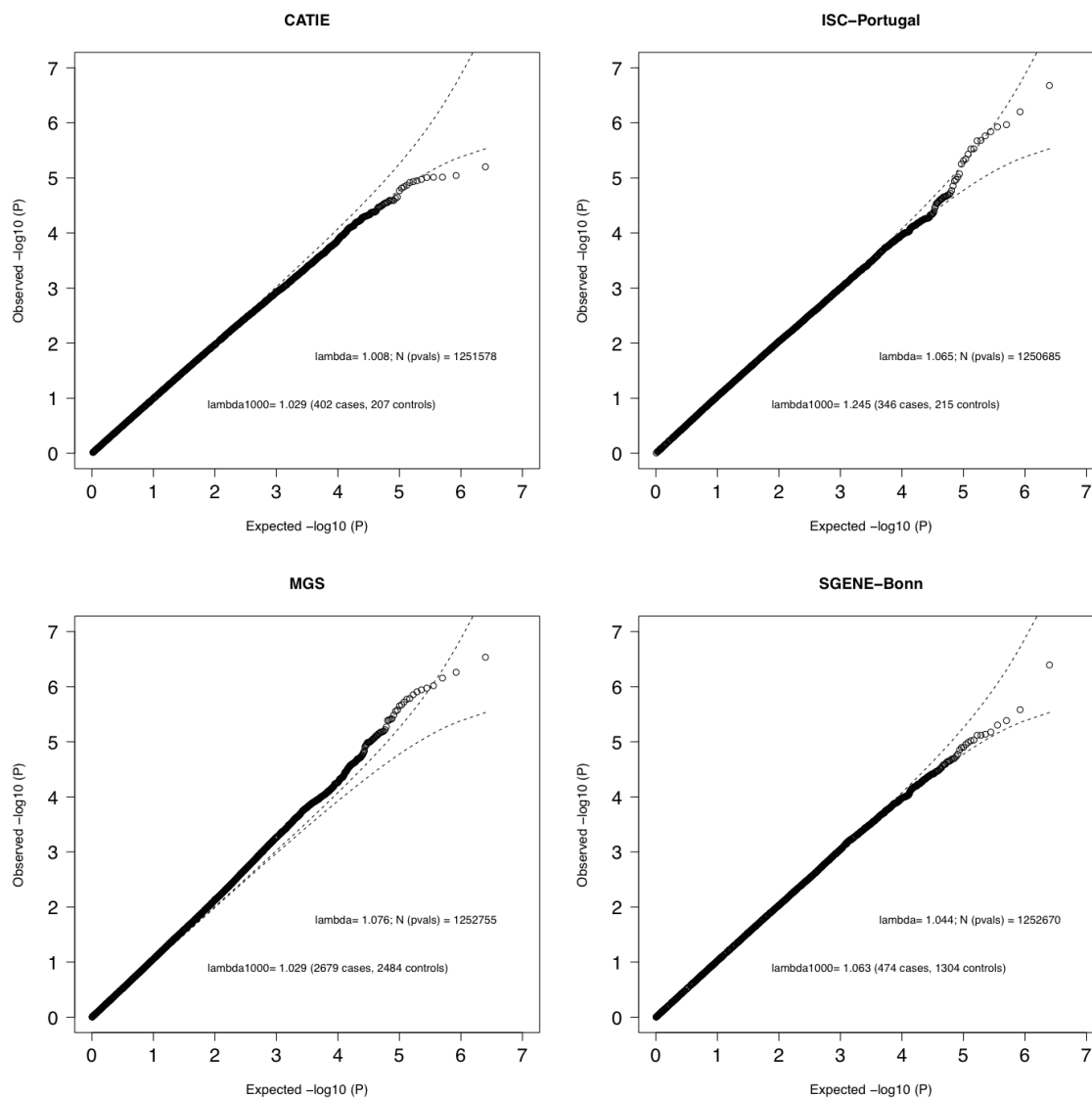


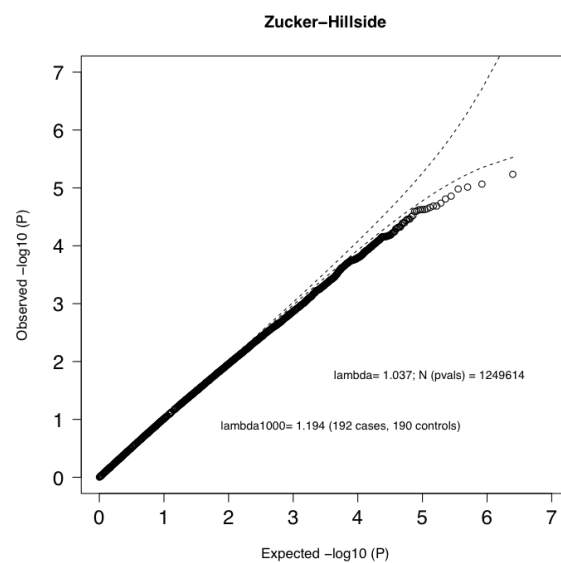
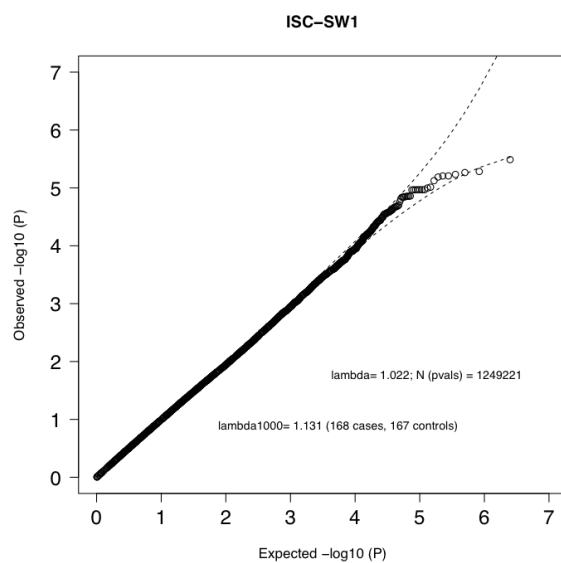
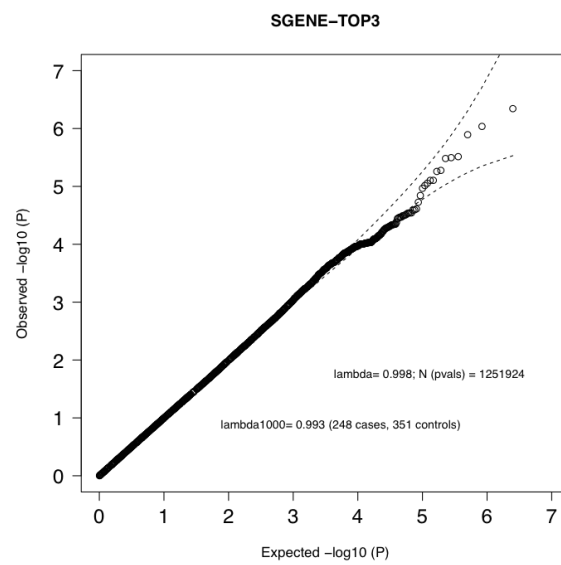
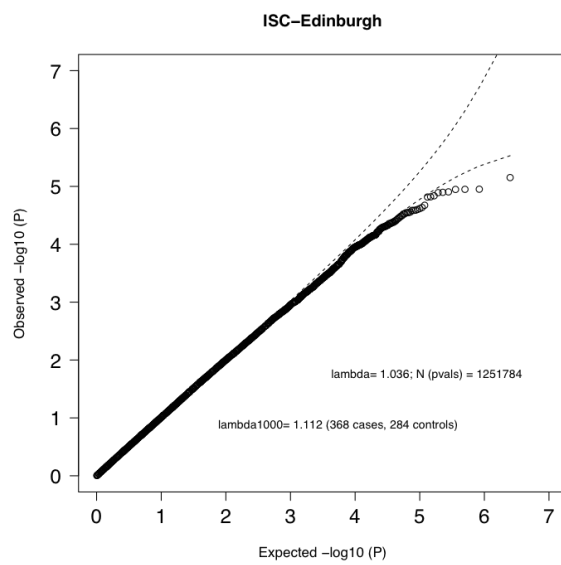


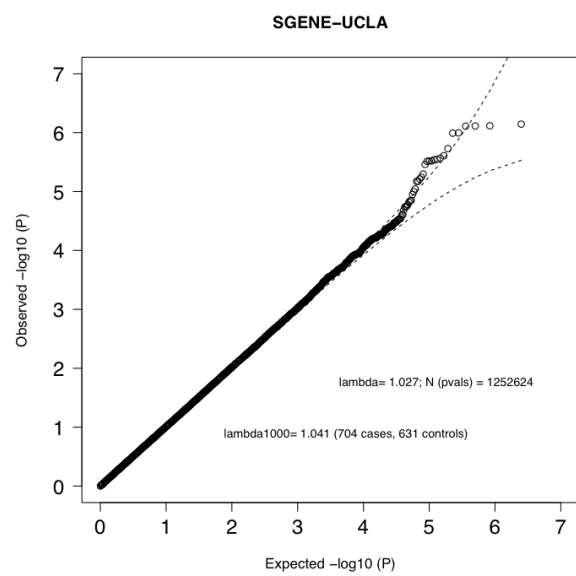
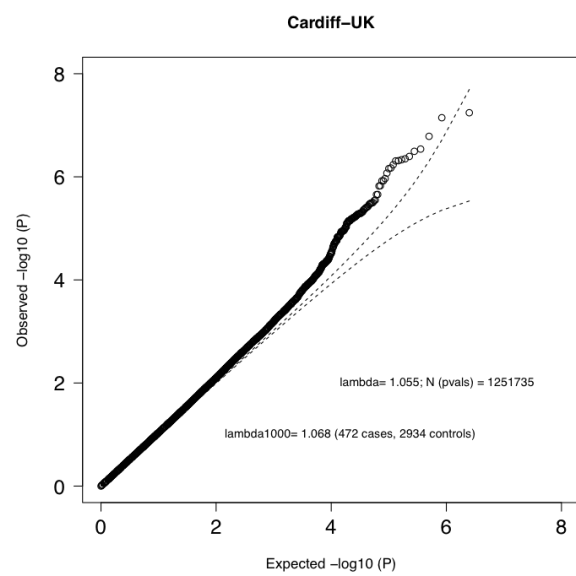
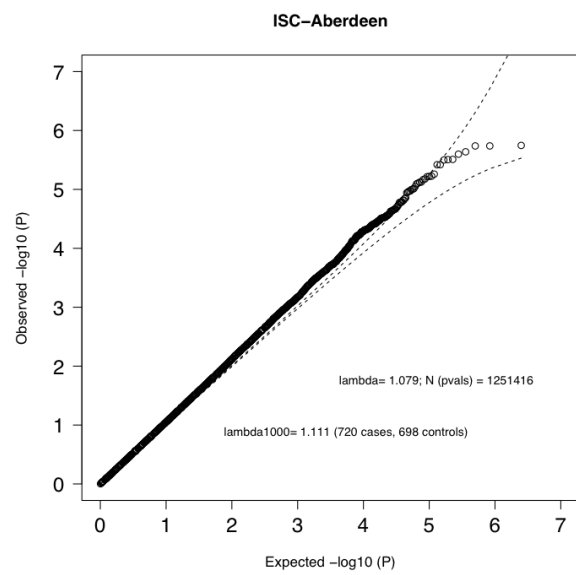
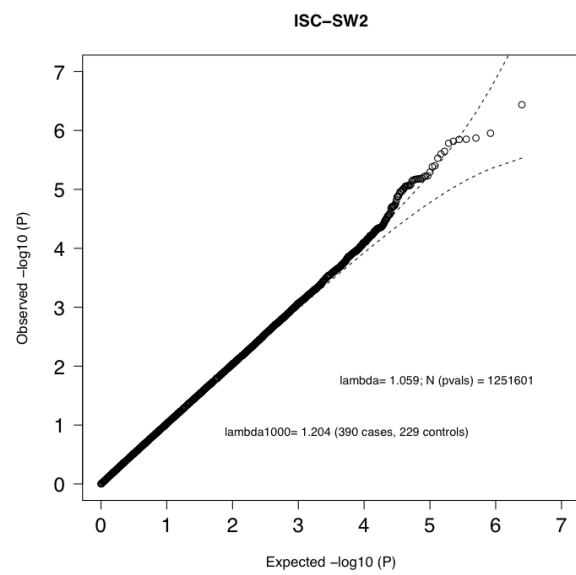
**Figure S9: Scatterplot of  $p$ -values from stricter outlier-exclusion vs. not, for mega-analysis (including study indicators) on log-scale.** Pearson's and Spearman's correlation coefficients are shown in the subtitle. SNPs from Table 2 are shown in red. See section A3a.

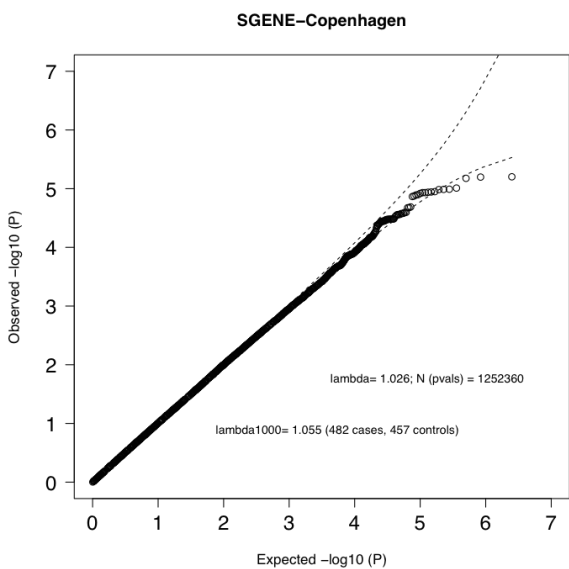
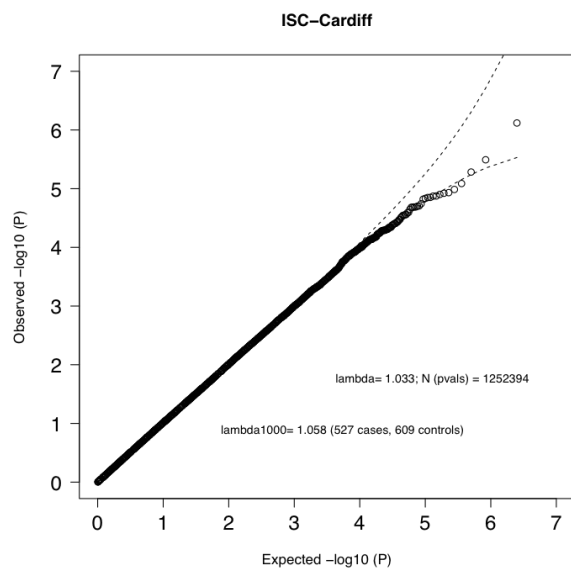
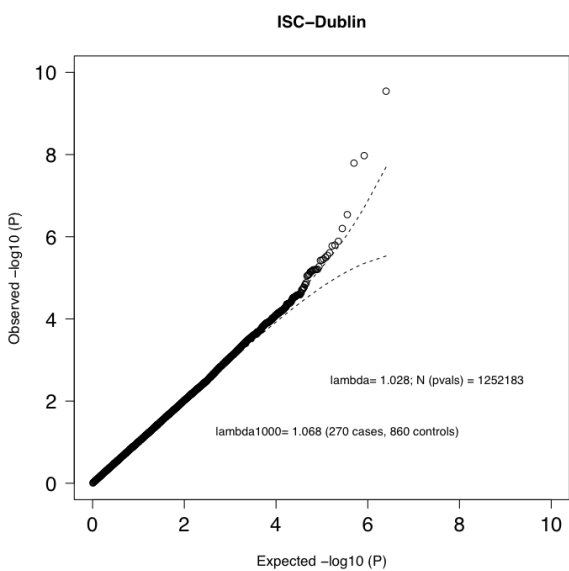
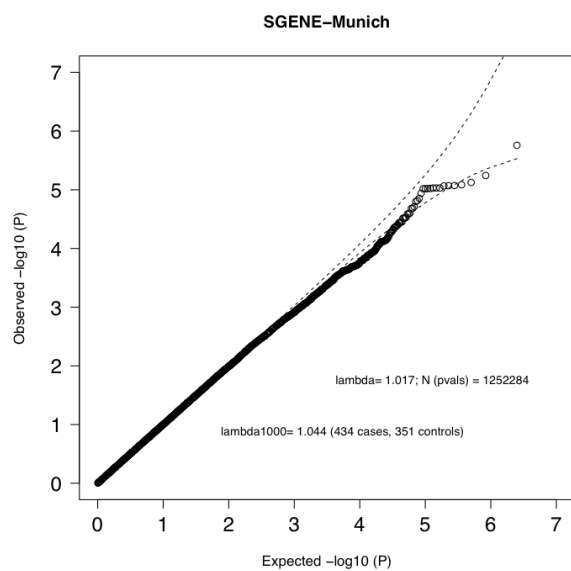


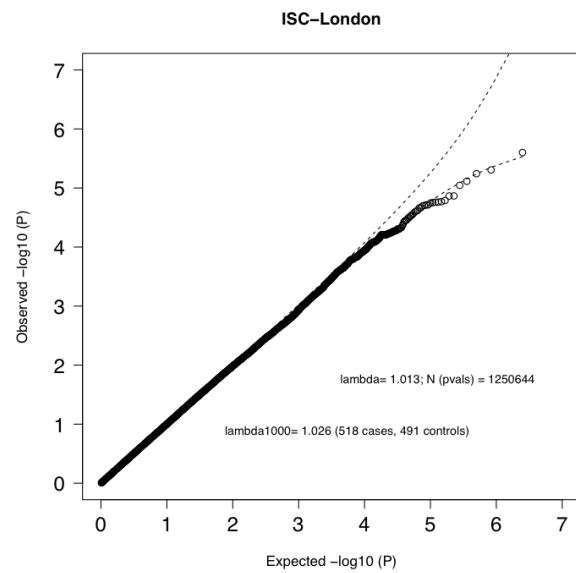
**Figure S10: Quantile-Quantile Plots for Individual Stage 1 Samples.** The observed distribution of the  $-\log_{10}$  of nominal  $p$ -values (y-axis) versus the expected (x-axis) are plotted for individual Stage 1 samples.





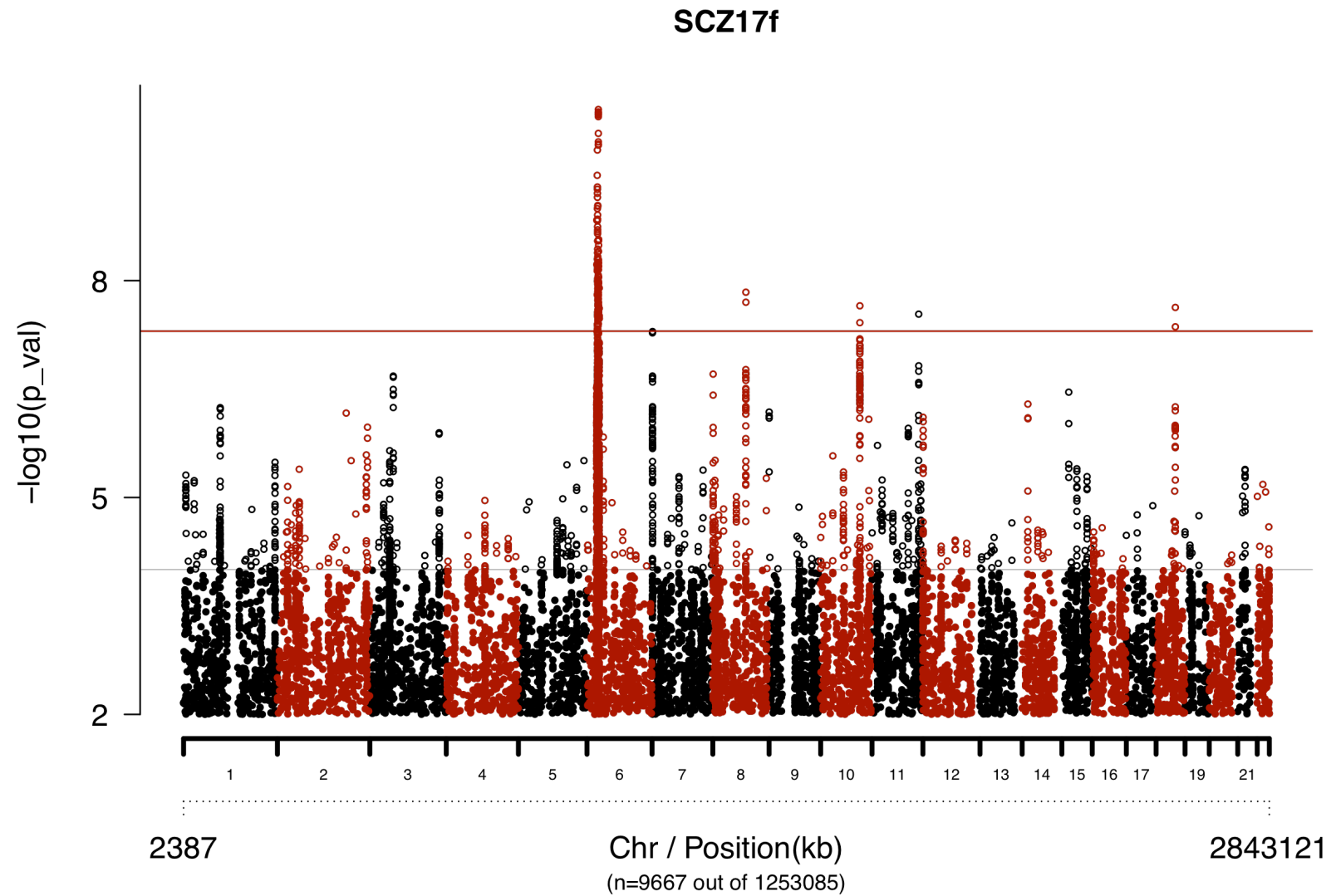


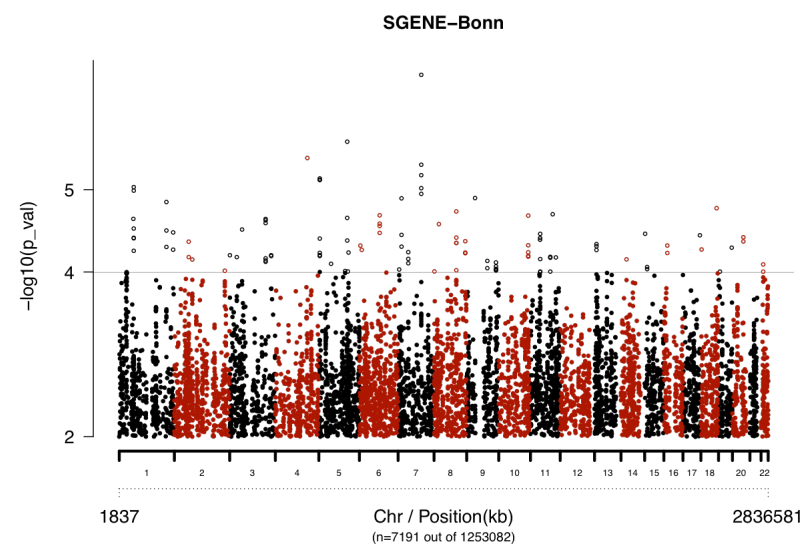
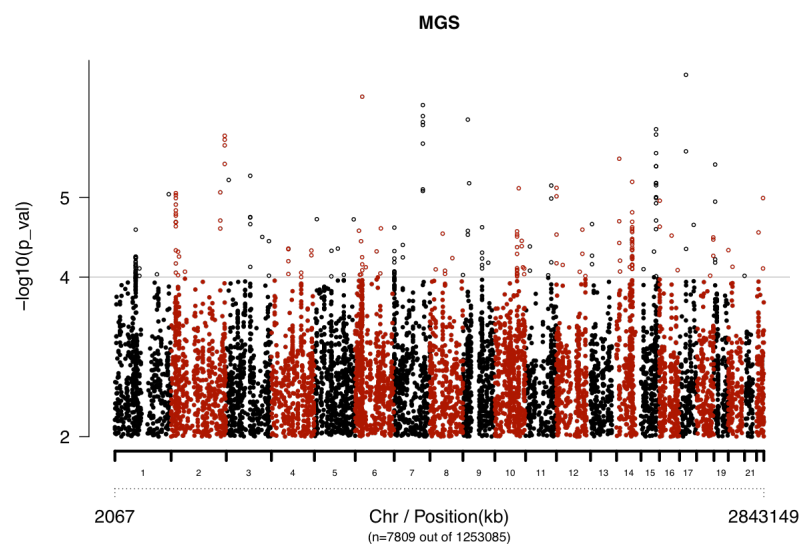
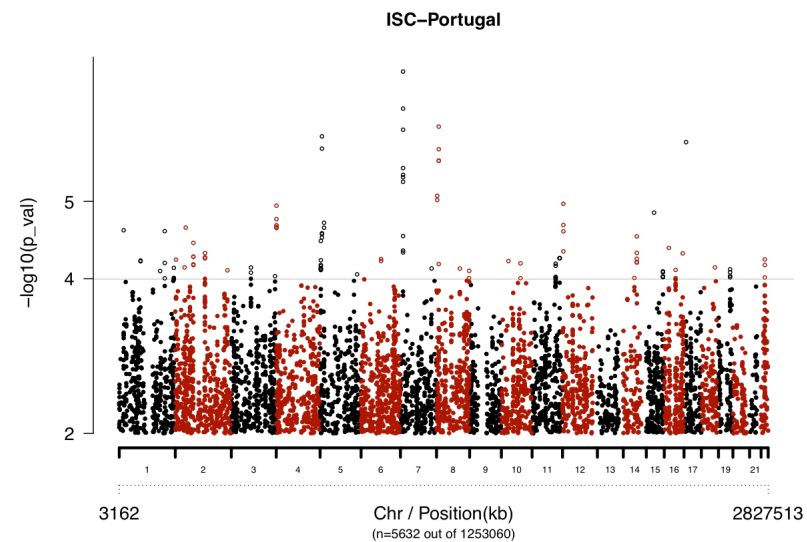
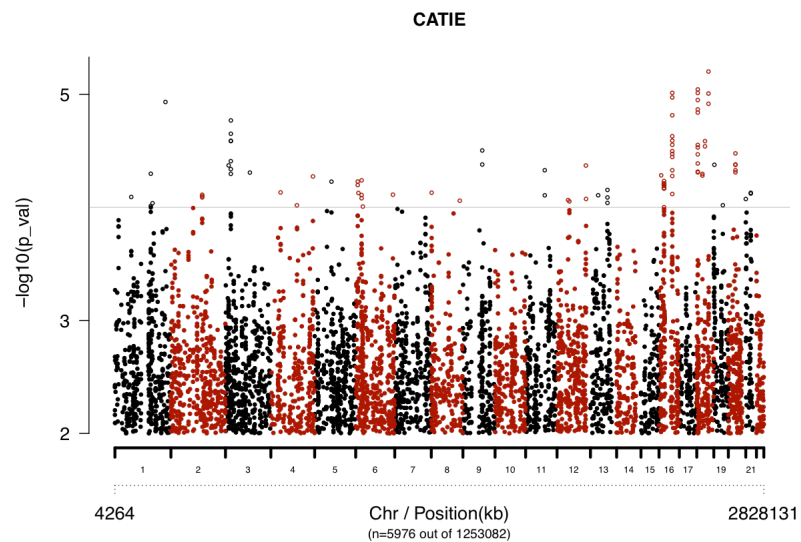


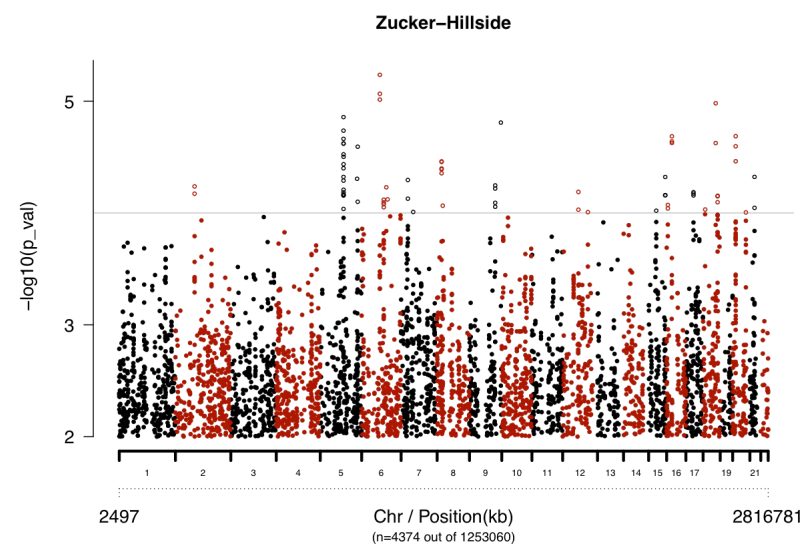
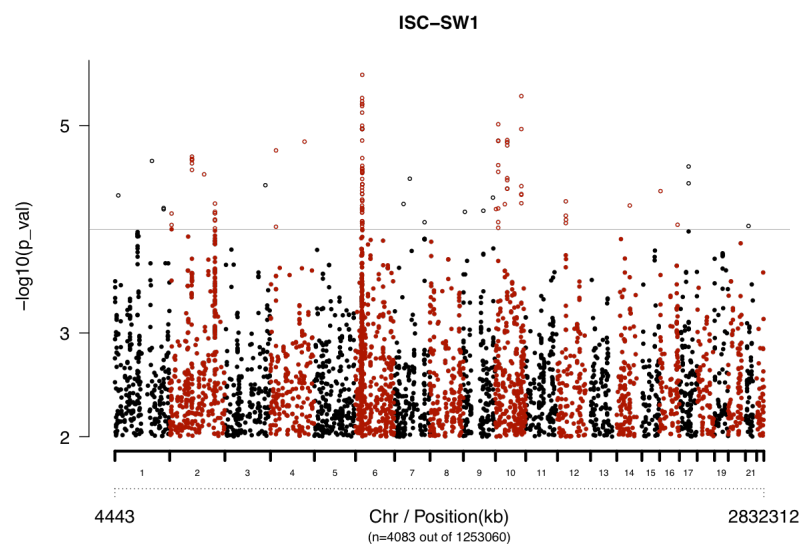
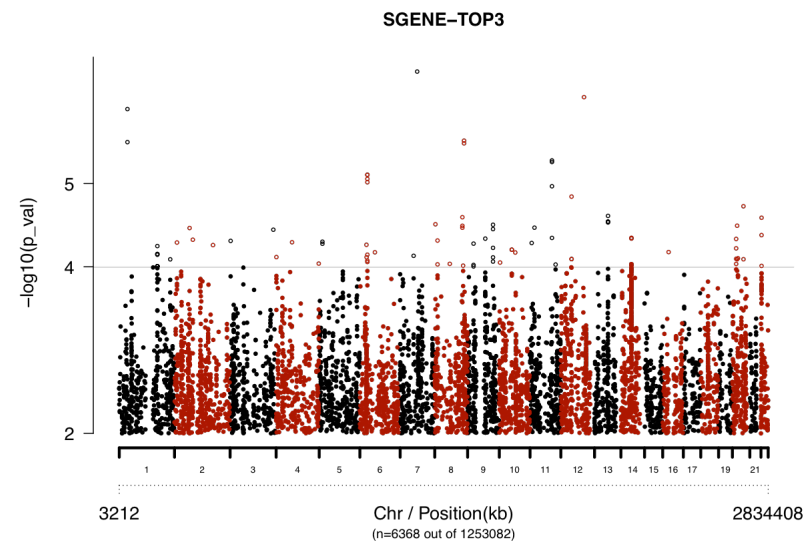
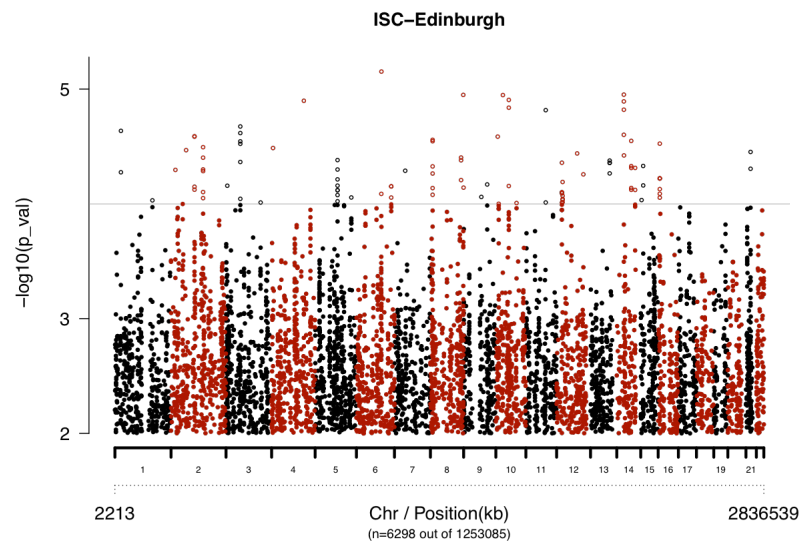


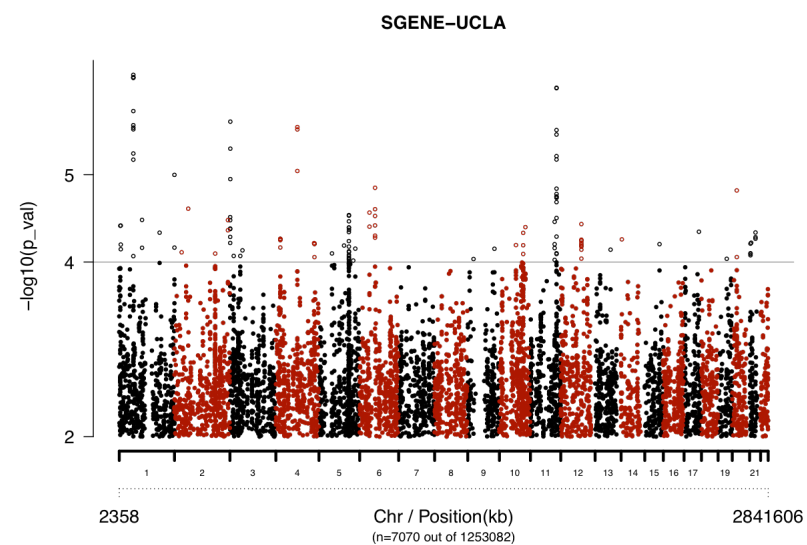
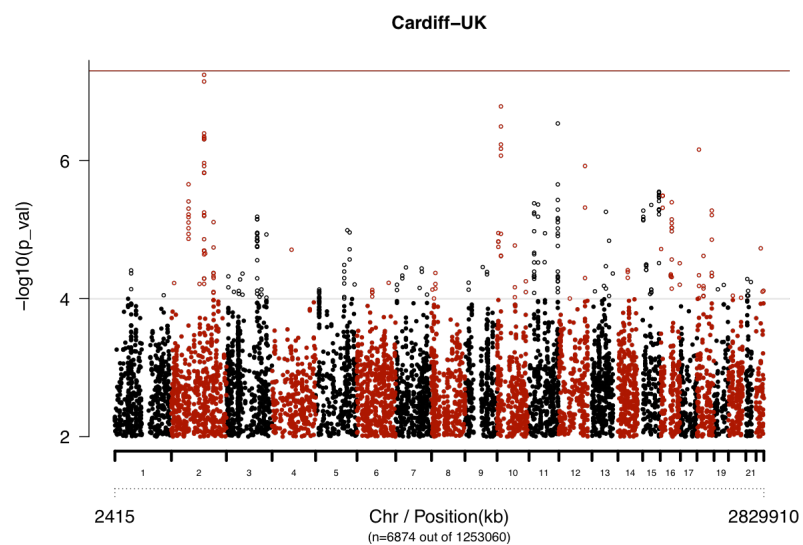
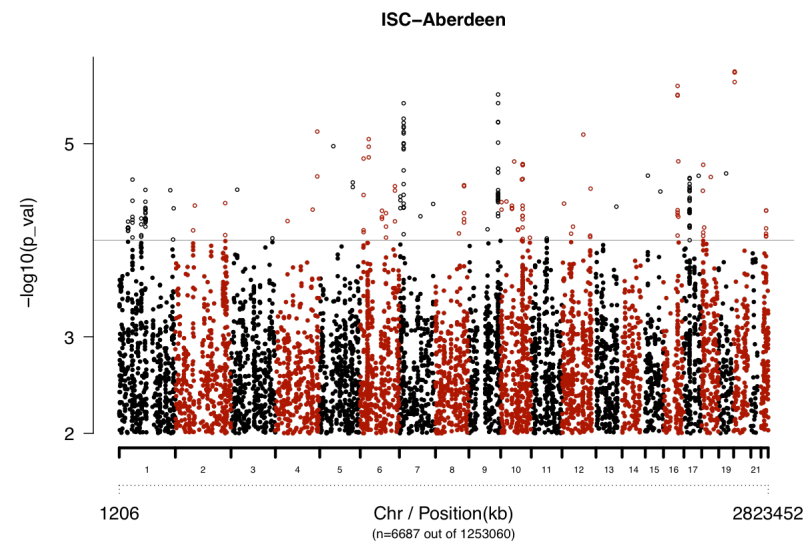
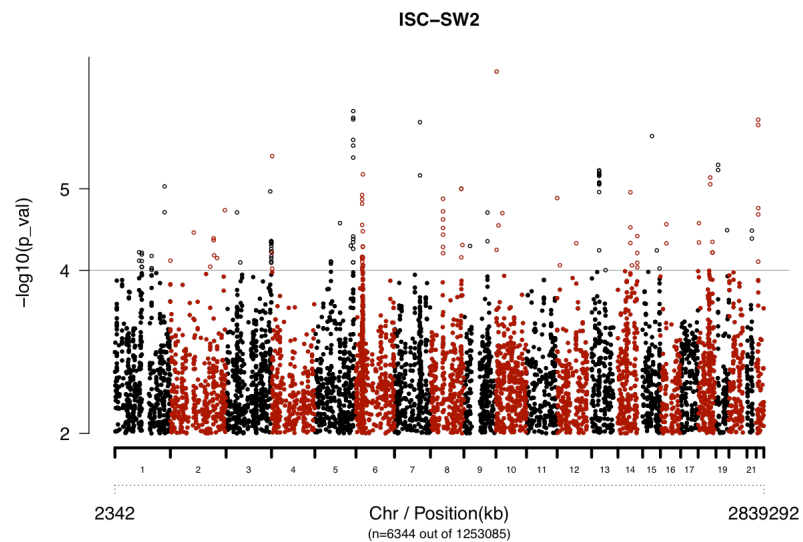


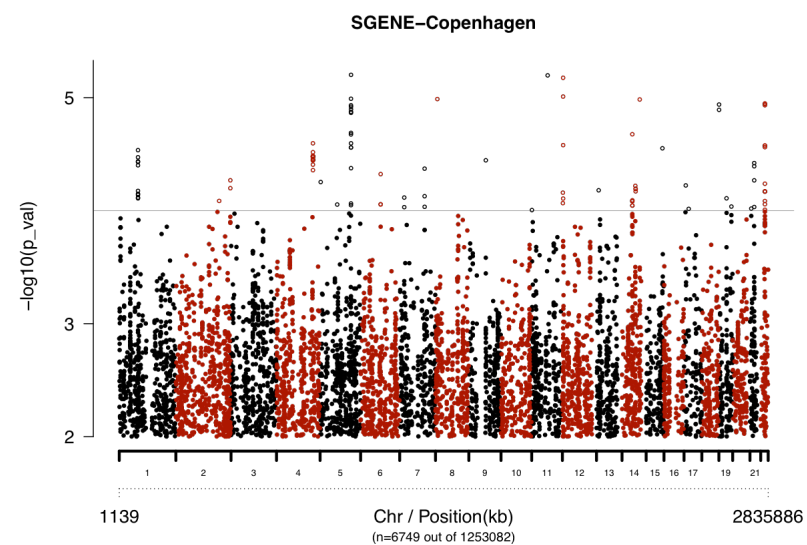
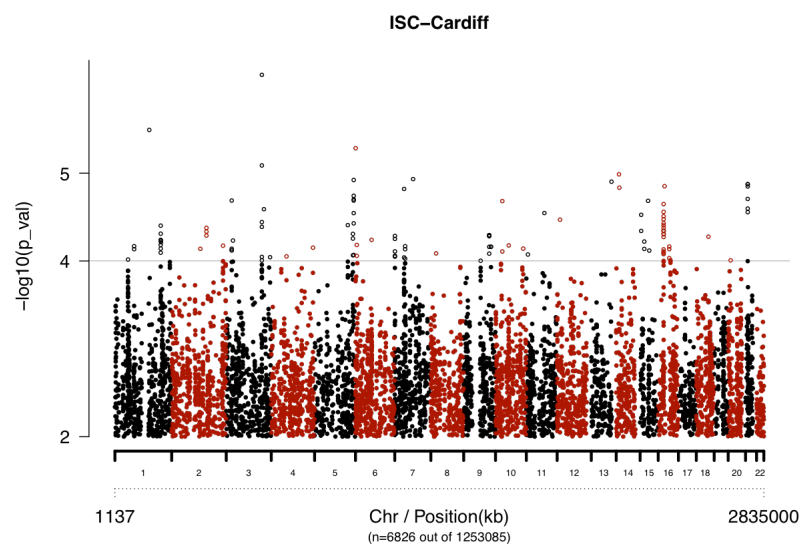
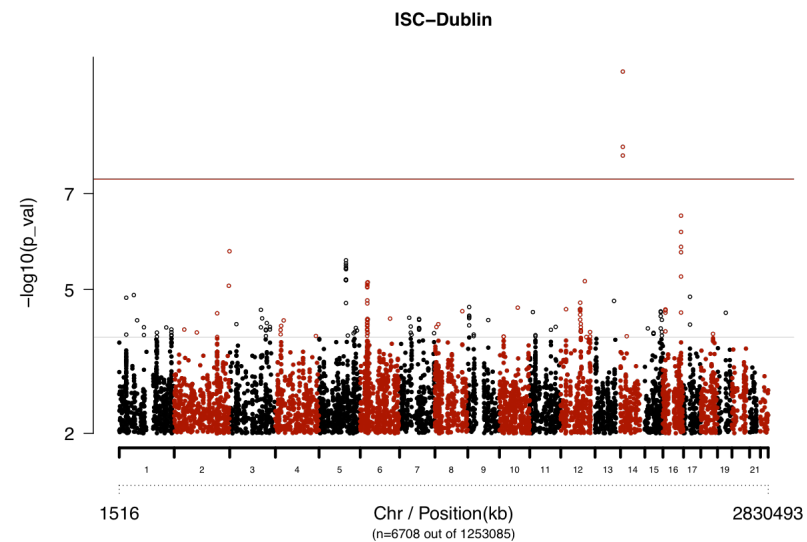
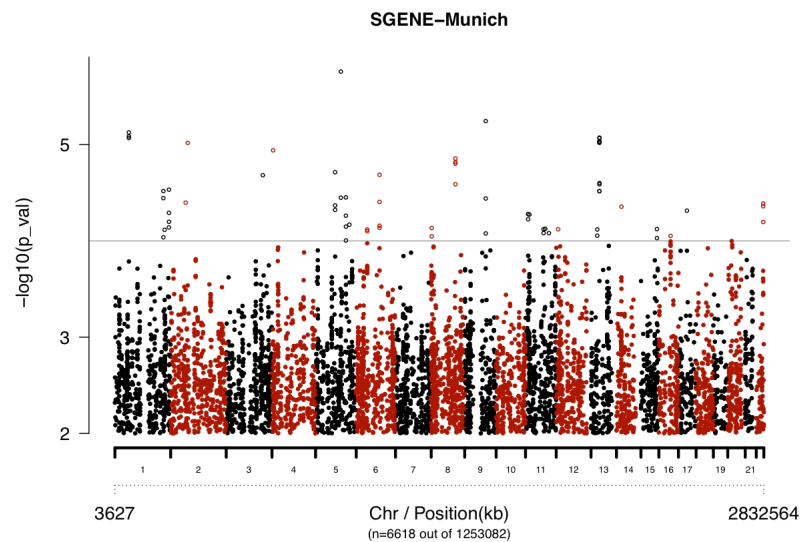
**Figure S11: Manhattan Plot - Stage 1 Individual Samples.** Standard  $-\log_{10}(p\text{-value})$  plot of the study results. Stage 1 results are first displayed for the entire sample, and then for each of the 17 individual samples.



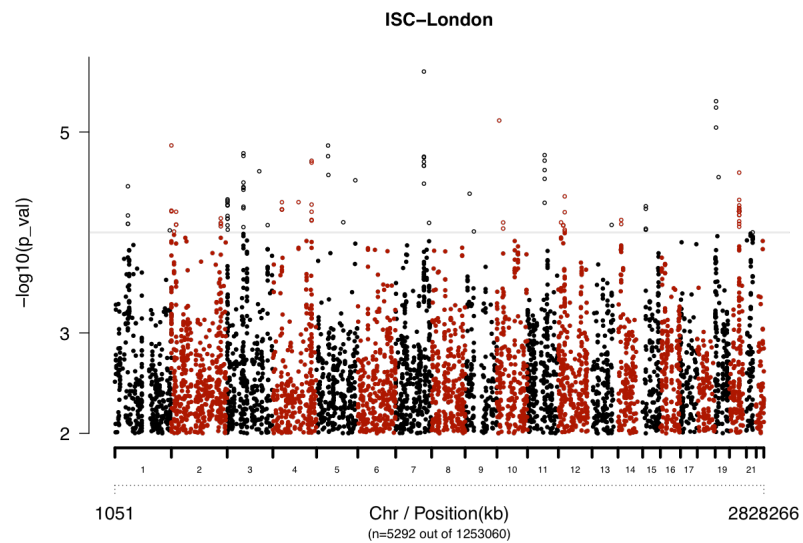




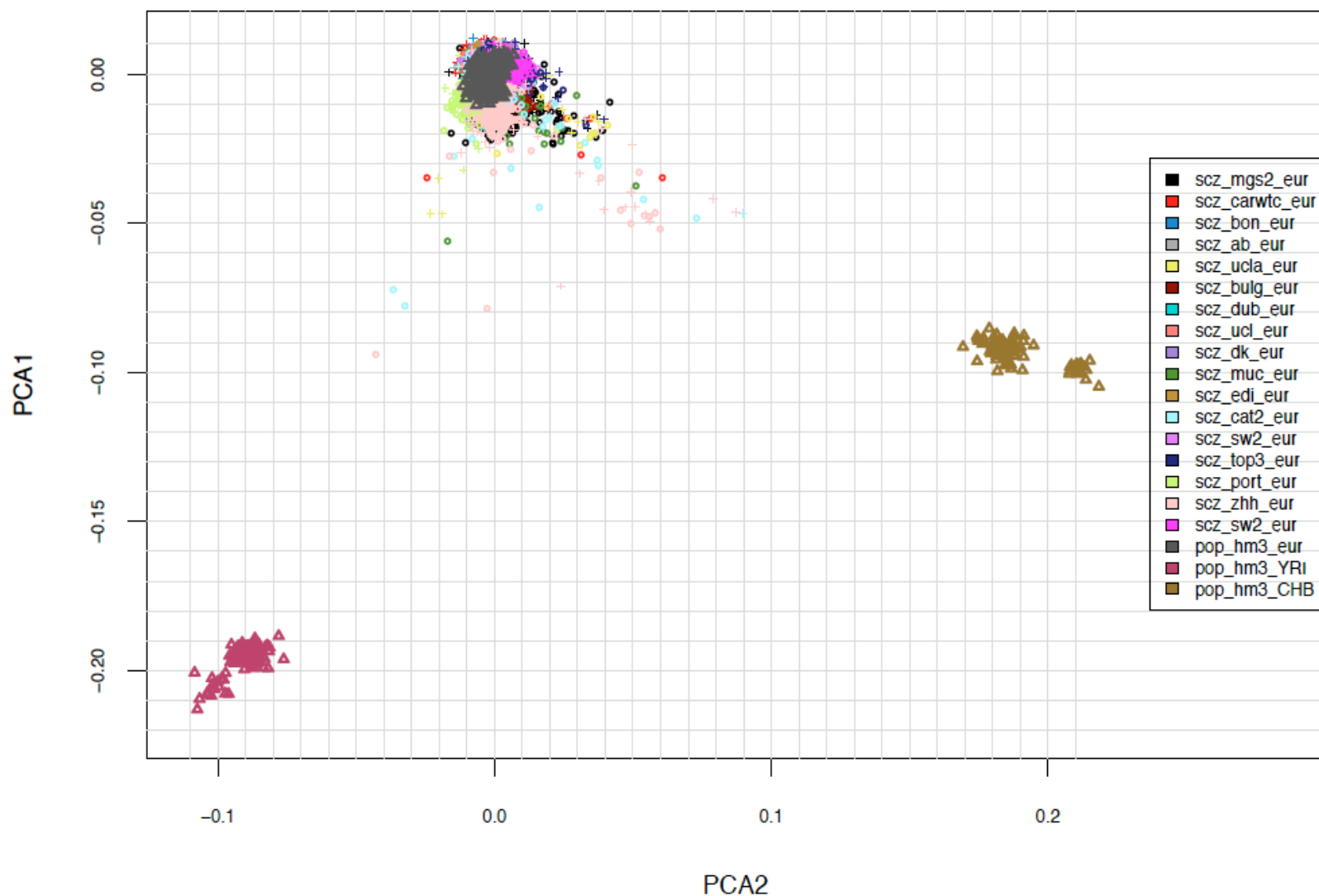








**Figure S12: Multi-Dimensional Scaling for all Stage 1 Samples and HapMap3.** Scatterplot of the first two principal components of all 17 Stage 1 samples is overplotted with three distinct HapMap3 populations (triangles: CEU/TSI, YRI, CHB), controls (plus signs), and cases (circles). As seen, the vast majority of the case and control Stage 1 samples fall within the European cluster.



## **E. Supplementary Tables**

The following supplementary tables below are presented as separate worksheets in one xls file:

**Supplementary Table 1: Stage 1 GWAS Samples - Ascertainment, Phenotyping, and Demographics.**

**Supplementary Table 2: Stage 2 Replication Samples - Ascertainment, Phenotyping, and Demographics.**

**Supplementary Table 3: Stage 1 Sample QC.**

**Supplementary Table 4: Genomic Regions Containing  $\geq 1$  SNP with  $p < 1E-05$  for Stage 1 Association.**

**Supplementary Table 5: Conditional Analyses.**

**Supplementary Table 6: Association Results for SNPs advanced to Stage 2.**

**Supplementary Table 7: Genome-Wide Significant Loci.**

**Supplementary Table 8: 17 genes (our of 301 predicted *MIR137* targets) with  $\geq 1$  "hotspot" of  $p < 1E-04$ .**

**Supplementary Table 9: Results of score analysis of aggregate effects of common SNPs.**

**Supplementary Table 10: Notable genes in highly significant regions (GWS or selected for replication) in PGC-SZ analyses, contrasted with BP and ASD findings.**

**Supplementary Table 11: Joint analysis of PGC-SZ and PGC-BP datasets.**

**Supplementary Table 12: Power Analyses for Stage 1 (GWAS Discovery).**

**Supplementary Table 13: Data Collection Procedures for Schizophrenia GWAS Studies.**

**Supplementary Table 14: Interaction Analysis of Table 2 SNPs.**



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## F. Supplementary References

1. Kendler, K.S. et al. The Roscommon Family Study. I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch. Gen. Psychiatry* **50**, 527-540 (1993).
2. Faraone, S.V. et al. Diagnostic accuracy and confusability analyses: an application to the Diagnostic Interview for Genetic Studies. *Psychol Med* **26**, 401-410 (1996).
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